University of Alberta

MATHEMATICAL MODELING OF LEUKEMIA AND TUMOR TREATMENT USING COMPETITION THEORY

by

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This thesis is dedicated to
Herb I. Freedman
with whom I had the good fortune to study on my doctorate program, who epitomized research, learning and scholarship, who instilled both the excitement and integrity of the research process, and who unselfishly promoted the scholarship of his students.

Abstract

This thesis deals with some mathematical models concerning the treatment of leukemia and tumors, respectively. The thesis comprises five chapters, the first of which is an introductory chapter, and the remaining four each contain a model for either leukemia or tumor treatment. The proposed models are analyzed for their stabilities and dynamical behaviors, both analytically and numerically, with biological interpretations.

In chapter two, from the viewpoint of biological stoichiometry, a mathematical model of vascular tumor treatment with chemotherapy techniques is proposed utilizing a system of delayed differential equations. Sufficient criteria are obtained for the uniform persistence of populations and the extinction of cancer cells. Conditions for the global stabilities of the cancer-free equilibrium and the interior equilibrium are obtained. Necessary and sufficient conditions for Hopf bifurcation to occur is also obtained by using the time delay as a bifurcation parameter.

Chapter three utilizes a logistic growth model to construct the cancer interactions with healthy tissue as a competition process and then extends to the diffusion case to model the spread of cancer within a site such as leukemia in the bone marrow. The existence, uniqueness, and boundedness of the solutions are established by means of a comparison principle and a monotonicity method. Persistence criteria for the normal cells and cancer cells are also derived.

With respect to the dynamical progression of chronic myeloid leukemia, chapter four utilizes a logistic-like growth model with self-regulated properties to construct the cytokinetics of cancer and normal cells as a competition process. The stabilities for the complicated system with one or two delays are fully analyzed and necessary and sufficient conditions for stability switches to occur are obtained.

Finally, this thesis studies the cycle-specificity of chemotherapy to the G_0 model. Stabilities of cancer-free equilibria are fully analyzed and conditions for stability switching and its biological implications are given. Also, necessary and sufficient conditions for Hopf bifurcation to occur are derived by using the time delay as a bifurcation parameter.

The mathematical techniques involved in the thesis include competition theory, persistence theory, comparison theory, dissipativity theory, spectrum theory, bifurcation theory and the complex analysis residual theory.

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1 Introduction

1.1 Mathematical modeling and cancer treatment

All organs of the body are made up of cells. Bio-medically, each tissue in a person can be defined as a cellular configuration of matter, endowed with a unique morphologic, pathologic, genetic and physiologic parametric configuration. This dynamic parametric configuration represents the state of health and well being of a person. The number and type of cells in each tissue is highly regulated. However, when this regulatory balance is altered, a variety of diseases, including cancer, can develop.

Cancers threaten an individual's life when their growth disrupts the tissues and organs needed for survival. Basically, there are four major types of cancer treatments used in an effort to obtain long-term periods of disease-free remission. The treatment types include surgery, radiation therapy, chemotherapy, and immunotherapy. These therapies can be used either alone or in combination with each other. Depending on location, size and stage of the tumor, as well as individual overall health, a treatment or treatments will be chosen to treat a cancer patient. Surgery is the oldest form of cancer treatment and only treats one particular part of the body. Therefore, people whose cancer has spread to another part of their body will not always be offered a surgery. Radiation therapy involves using large

doses of high-energy beams or particles to destroy cancer cells in a specifically targeted area. Most commonly, localized solid tumors, leukemia and lymphoma are treated by radiotherapy; for some, it will be the only cancer treatment they need, but often, radiation is used in combination with other treatments, in which radiation shrinks the tumor to make surgery or chemotherapy more effective. Chemotherapy involves utilizing powerful drugs to destroy cancer cells and inhibit their growth. Chemotherapy might involve one drug, or a combination of two or more drugs, depending on the type of cancer and its rate of progression. In order to improve the treatment of cancer, chemotherapy might be used in combination with other treatments such as surgery or radiation, to make sure all cancer cells have been eliminated. Immunotherapy is body's own natural defenses to fight cancer and works as the body's first line of defense against disease. Generally, white blood cells in the body can be stimulated in several ways to boost the body's immune response to cancer, with little or no effect on healthy tissue. Also, immunotherapy can be used to lessen the side effects of other cancer treatments. All in all, with the exception of surgery, which relies mostly on the accuracy of x-rays and other imaging techniques, the other treatments such as chemotherapy and immunotherapy mainly depend on accurate staging of the tumor, the dynamical properties of the tumor, the optimal administration of the anti-cancer drugs, and the kinetic interactions among tumor, host and drug.

Clinically, it is observed that every pathological process, including carcinogenesis, possesses a time evolution profile. Thus, if the kinetic parameters characterizing a pathological process such as cancer can be determined accurately, it will be possible to establish quantitative therapeutic criteria depicting the prognosis or outcome of therapy. When applying therapy, it may disturb and alter the initial pathological parametric configuration of the cancer cells. Under such situations, it may be prudent to use mathematical modeling and analysis to (1) make quantitative predictions regarding the dynamic evolution of the disease and the region of therapeutic efficacy, and (2) provide a more rational basis for the design of a drug protocol based on the mathematical relation between the dynamical variables involved in the progression of disease, and finally (3) determine the general prognosis of the cancer based on the initial data and the clinical parametric configuration of the cancer patient and the pharmacodynamics of the anti-cancer

drug. In short, mathematical models based on biological principles serve to define critical underlying dynamics and interactions in the complex systems and predict the results of system perturbations through therapy.

Now with the advent of modern experimental equipment and the desire to obtain quantitative therapeutic criteria, computerized mathematical modeling has become an important part of clinical cancer research. The use of computer simulations helps many physicians design the safest and most efficient treatments in terms of drug and schedule choices. The simulations allow both the mathematicians and the medical oncologists to observe model behavior graphically. In particular, the simulations of pharmacodynamics models quantifying drug effects on several target tissues allow physicians to observe the short/long-term cellular dynamics of specific patients undergoing drug therapy, and provide them efficient treatments such as per-case choice of drug, drug combinations and schedules to achieve clinically desired end-points. Mathematical models could be deterministic or stochastic. Basically, the two approaches describe the same basic dynamics. Stochastic modeling is used if there is randomness or uncertainty about the evolutionary process. But if there is abundance of experimental kinetic data and established physiological pathways and mechanisms on a given pathological process, it is possible to use deterministic modeling techniques. In this thesis, deterministic modeling will be used to describe cancer chemotherapy and immunotherapy and simulate the models under various parametric configurations and finally completely predict the output of the models if the input parameters and initial states of the model are given.

1.2 Cancer: tumor & leukemogenesis

In simple terms, cancer is a group of more than 100 diseases that develop across time and involve the uncontrolled growth regulatory mechanisms of the body.

Cancerous tumor growth can be considered as having an avascular phase and a vascular phase. During the avascular phase, the tumor is of such a size that the surface to volume ratio of the spheroid is adequate for diffusion of nutrients and oxygen, and consequently there is a rapid exponential growth. During the later stages of avascular growth, the tumor growth decelerates and at a certain critical cell number, the growth levels off into a plateau

as cellular proliferation ia balanced by cell death, and necrosis due to lack of oxygen and nutrients[102]. A state dormancy occurs unless the tumor acquires new blood vessels by a process called vascularization and tumor angiogenesis. Tumor angiogenesis enables an aggregate of tumor cells to expand beyond the maximal three dimensional size restraints imposed by space, nutrients and oxygen diffusion requirements. The primary tumor may then metastasize into other organs of the human anatomy forming secondary tumors. After neo-vascularization the primary tumor may again undergo exponential growth unless it encounters limitations. Thus realistic tumor growth may be a cascade of exponential growths interspaced with deceleratory periods or dormant growth. However many other realistic growth scenarios are possible such as modeled by Goldman et al[44]. But generally logistic growth or Gompertz tumor growth profiles are the most frequently used models to depict tumor growth.

Leukemia is a cancer of blood cells that originates in the bone marrow, the soft, spongy inner portion of certain bones. The cancerous cells in leukemia are the white blood cells (leukocytes). When a blood cell undergoes a bio-transformation into a malignant cell, leukemia begins to develop, in which the malignant cells begin to multiply in the marrow, and as they do so they crowd out the normal blood cells – those that carry oxygen to the body's tissues, fight infections, and help wounds heal by clotting the blood [49]. Leukemia can also spread from the marrow to other parts of the body, including the lymph nodes, brain, liver, and spleen.

Blood-cells develop from stem cells in the bone marrow. These primitive cells are capable of developing into any kind of blood cell. Each of these types of cells has a very specific job in the functioning of the body.

A malignant transformation can happen at any stage of blood cell development. When leukemia cells result from the transformation, they carry many characteristics of the cell from which they began. Most leukemia are either myelogenous leukemia or lymphocytic leukemia [49]. Physicians also classify leukemia according to whether they are acute or chronic. In acute leukemia, the malignant cells are blasts that remain very immature and incapable of performing their immune system functions. The onset of acute leukemia is rapid and the number of blasts increases rapidly. Chronic leukemia develop in more mature

cells, which can perform some of their functions but not well. These abnormal cells may increase at a slower rate than in acute leukemia. As a result, the disease gets worse more slowly than in acute leukemia.

Researchers have noticed an increasing proportion of younger patients with chronic myelogenous leukemia (CML) in recent years. Treatment approaches for adult leukemia may include chemotherapy and immunotherapy. Radiation therapy is sometimes used for leukemia in the central nervous system (see [49] for more information about leukemia).

1.3 Mathematical preliminaries: basic definitions and standard theorems

In this section of the introduction we will list all useful basic definitions and standard theorems which will be encountered in the forthcoming chapters.

1.3.1 Definitions of basic concepts

In this subsection we present the definitions of some basic concepts and parameters which will later be used in theorems or proofs of theorems in the forthcoming chapters.

Definition 1: Acyclicity [13]

Consider the system

$$\dot{x}(t) = F(x) \tag{1.1}$$

$$x(t_0) = x_0,$$

where $x_0 \in \Re_+^n$, $F \in C(\Re_+^n, \Re^n)$, $\Re_+^n = \{x \in \Re^n | x_i \geq 0, 1 \leq i \leq n\}$ and $\bar{\Re}_+^n = cl\Re_+^n$ denotes the closure of $\Re_+^n$.

Let M_1 and M_2 be any isolated invariant sets on the boundary of $\Re_+^n$, denoted by $\partial\Re_+^n$. Let $\gamma(x)$ denote the orbit of a point $x \in \partial\Re_+^n$ such that

$$\alpha(x) = M_1, \ \omega(x) = M_2,$$

respectively the alpha and omega limit sets of x.

Then M_1 is said to be connected or chained to M_2. This is depicted symbolically by

$$M_1 \rightarrow M_2.$$

A finite sequence $M_1, M_2, \cdots, M_k$ of isolated invariant sets of (1.1) will be called a chain if

$$M_1 \to M_2 \to \cdots \to M_k (M_1 \to M_1 \ if k = 1).$$

The chain will be called a cycle if $M_k = M_1$. If the dynamics are such that there are no cycles, system (1.1) is said to be acyclic.

Definition 2: Dissipativity [13,40]

Consider system (1.1) and let

$$x(t) = \{x_i(t)\}_{i=1}^n.$$

Then the system describing the evolution of $x(t)$ is called dissipative if

$$\limsup_{t \to \infty} ||x(t)|| \leq L,$$

where L is a positive constant. In particular, it implies that the trajectories of the system are asymptotically bounded. In other words, there is a compact neighborhood $B \subset \bar{\Re}_+^n$ such that for sufficiently large $T = T(t_0, x_0)$

$$x(t) \in B, \ t \geq T,$$

where $x(t)$ is any solution of system (1.1) such that $x(t_0) = x_0$ in $\Re_+^n$.

For dissipative systems, the existence of an equilibrium in the interior of $\Re_+^n$, denoted by $int\Re_+^n$, is a consequence of uniform persistence [12,13].

Definition 3: Hyperbolicity [12,13]

Let $E(x_0) \in \Re_+^n$ such that $F(E(x_0)) = 0$ for system (1.1). Then $E(x_0)$ is a critical point of system (1.1).

The linearization of (1.1) in the neighborhood of $E(x_0)$ gives the equation

$$\dot{y}(t) = DF(E(x_0))y \tag{1.2}$$

$$y(t_0) = y_0, \ y \in \Re_+^n,$$

where $J_{E(x_0)} = DF(E(x_0))$ is the Jacobian matrix of the linearization via a Taylor expression around $E(x_0)$. In particular, $J_{E(x_0)}$ is defined as

$$J_{E(x_0)} = \begin{bmatrix} \frac{\partial F_1(x)}{\partial x_1} & \cdots & \frac{\partial F_1(x)}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial F_n(x)}{\partial x_1} & \cdots & \frac{\partial F_n(x)}{\partial x_n} \end{bmatrix}.$$

The eigenvalues of $J_{E(x_0)}$ are defined by the set

$$\sigma(J_{E(x_0)}) = \{\lambda | det(J_{E(x_0)} - \lambda I) = 0\}.$$

The critical point $E(x_0)$ or periodic orbit $x = \psi(t)$ is called hyperbolic respectively if the eigenvalues corresponding to $J_{E(x_0))}$ or the Floquet exponents for $\psi(t)$ are such that they have *nonzero* real parts. Furthermore, let $\sigma(J_{E(x_0)})$ contain n eigenvalues. Then:

(1) $E(x_0)$ is a hyperbolic *saddlepoint* if there exist some $\lambda_i \in \sigma(J_{E(x_0)})$ with $Re\lambda_i > 0$ and also some $\lambda_j \in \sigma(J_{E(x_0)})$ such that $Re\lambda_j < 0$, for $i, j \in \{1, 2, ..., n\}$, but there exist no λ_k such that $Re\lambda_k = 0$.

(2) $E(x_0)$ is a hyperbolic *sink* if for all $\lambda_i \in \sigma(J_{E(x_0)})$ we have $Re\lambda_i < 0$, $i = 1, 2, .., n$.

(3) $E(x_0)$ is a hyperbolic *source* if for all $\lambda_i \in \sigma(J_{E(x_0)})$, we have $Re\lambda_i > 0$, $i = 1, 2, ..., n$.

Definition 4: Isolatedness [30]

Consider system (1.1) and let $F(x)$ be analytic and let $E_i(x_i)$ for $i \in \{0, 1, .., n\}$ denote the critical points of (1.1). $E_0(x_0)$ is said to be isolated if the Jacobian matrix due to linearization of system (1.1) in the neighborhood of $E_0(x_0)$, denoted by $J_{E_0(x_0)}$ is such that $J_{E(x_0)}$ is non-singular.

In the results presented in the forthcoming chapters, isolatedness and acyclicity will be guaranteed by the hyperbolicity and global asymptotical stability requirements for the critical points in their respective two or three dimensional subspaces.

Definition 5: Persistence [12,13,31,36]

Consider system (1.1) and let

$$x(t) = \{x_i(t)\}_{i=1}^{n}.$$

Then $x_i(t)$ is said to be persistent if

$$x_i(t) > 0,\ t \geq 0,\ \liminf_{t \to \infty} x_i(t) > 0.$$

Further, the persistence is said to be uniform, if

$$\exists \delta > 0,\ \ni \liminf_{t \to \infty} x_i(t) > \delta,$$

independent of initial conditions $x_i(0)$.

System (1.1) is said to be (uniformly) persistent if each component x_i, $i = 1, 2, .., n$ is (uniformly) persistent.

In particular, persistence of system (1.1) corresponds to global survival of all x_i, $i = 1, 2, .., n$, non-persistence corresponds to local extinction of at least one component.

Definition 6: Permanence [58]

System (1.1) is said to be permanent if there exists a compact region $\Omega_0 \in int\Re^n_+$ such that every solution of system (1.1) with nonnegative initial conditions will eventually enter and remain in region Ω_0.

Clearly, for a dissipative system uniform persistence is equivalent to permanence.

Definition 7: Liapunov functions and negative definiteness[5,39,61,91]

Consider system (1.1) such that

$$F : C(\Re^n_+) \longrightarrow \Re^n.$$

Let D be any neighborhood in $\Re^n_+$. Then V is a Liapunov function for system (1.1) on D if

(1) $V \in C^1(D)$ and bounded below,

(2) $V(\bar{x}) = 0$, where $F(\bar{x}) = 0$, and $\bar{x}$ is in the interior of D,

(3) there exists an $\delta > 0$ such that $V(x) > 0$ whenever $x \in B_\delta(\bar{x})\backslash\bar{x}$, where

$$B_\delta(\bar{x}) = \{x \in D : ||x - \bar{x}|| < \delta\},$$

(4) $\dot{V}(x) \leq 0$ along the solution trajectories of system (1.1), $x \in D \setminus \{\bar{x}\}$,

(5) $V(x) \to \infty$ if either $||x|| \to \infty$, or $x \to \partial D$.

Remarks

(i) The requirements (2) and (3) of $Defintion7$ imply that V is positive definite.

(ii) For global asymptotic stability, we require $\dot{V}(x) < 0$.

(iii) If V and $-\dot{V}$ are positive definite with respect to $\bar{x}$, then $\bar{x}$ is globally asymptotically stable.

Now, assume $\dot{V}$ can be written in the form of

$$\dot{V} = X^T AX =< AX, X >,$$

where $X = (x_1 - \bar{x}_1, ..., x_n - \bar{x}_n)^T$, and $A(x, \bar{x})$ is a $n \times n$ symmetric matrix over $\Re$, given

by the expression

$$A(x,\bar{x}) = \begin{bmatrix} a_{11} & \dots & a_{1n} \\ \vdots & & \vdots \\ a_{n1} & \dots & a_{nn} \end{bmatrix}.$$

Let D_k denote the sequence of leading principal minors of the matrix $A(x,\bar{x})$. In particular,

$$D_1 = a_{11}, \quad D_2 = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix},$$

$$D_3 = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}, \ \dots, \ D_n = \begin{bmatrix} a_{11} & \dots & a_{1n} \\ \vdots & & \vdots \\ a_{n1} & \dots & a_{nn} \end{bmatrix}$$

Theorem 1.3.1 *The quadratic form $A(x,\bar{x})$ and consequently, $\dot{V} = X^T AX$ is negative definite if and only if the following inequalities hold:*

$$D_1 < 0, \ D_2 > 0, \ D_3 < 0, \ \dots, \ (-1)^n D_n > 0.$$

Theorem 1.3.2 *A necessary and sufficient condition for the quadratic form $A(x,\bar{x})$ to be negative definite is that all the characteristic roots (eigenvalues) of $A(x,\bar{x})$ are negative or have negative real parts.*

1.3.2 Standard theorems

Bendixon's Negative Criterion/ Bendixon-du Lac [11]

Theorem 1.3.3 *Consider the system*

$$\begin{aligned} \dot{x}_1(t) &= F_1(x_1, x_2) \\ \dot{x}_2(t) &= F_2(x_1, x_2) \end{aligned} \tag{1.3}$$

on a simply connected domain $D \subset \Re^2$. Suppose:

(i) $F_1, F_2 \in C^1(D, \Re)$ such that F_1, F_2 have continuous first partial derivatives $\frac{\partial F_1}{\partial x_1}, \frac{\partial F_2}{\partial x_2}$ on D.

(ii) $\frac{\partial F_1}{\partial x_1} + \frac{\partial F_2}{\partial x_2}$ does not change sign on D, and does not vanish identically in any open subset of D.

Then there are no nontrivial closed paths (periodic solutions, limit cycles) in D.

Theorem 1.3.4 *Suppose that,*

(i) $\exists B(x_1, x_2) \in C^1(D, \Re)$,

(ii) $\frac{\partial}{\partial x_1}[F_1(x_1, x_2)B(x_1, x_2)] + \frac{\partial}{\partial x_2}[F_2(x_1, x_2)B(x_1, x_2)]$ *does not change sign or vanish identically on any open subset of the simply connected domain* D.

Then there are no closed paths lying entirely in D.

(iii) If E *is an annular region contained in* D *on which* (ii) *does not change sign, then there is at most one limit cycle in* E.

Floquet Multipliers Theory [83]

Consider the non-autonomous system

$$\begin{aligned} \dot{x}(t) &= F(t, x) \\ x(t_0) &= x_0 \\ F(t + \omega, x) &= F(t, x), \end{aligned} \tag{1.4}$$

where $F \in C^1(\Re_+ \times \Re_+^n, \Re^n)$, $\Re_+ = [0, \infty)$, and $x, x_0 \in \Re^n$.

Let $\psi = (\phi_1(t), ..., \phi_n(t))$ be a given periodic orbit or limit cycle of (1.4). Let the Jacobian matrix of linearization of (1.4) about ψ be given by

$$J_\psi = DF(\psi) = \begin{bmatrix} m_{11} & \dots & m_{1n} \\ \vdots & & \vdots \\ m_{n1} & \dots & m_{nn} \end{bmatrix} =: M(t)$$

such that J_ψ is locally integrable.

The Floquet exponents are the eigenvalues of $X(\omega)$ where $X(t)$ solves

$$\dot{X}(t) = M(t)X(t), \;\; X(0) = I,$$

where

$$X(t) = \begin{bmatrix} X_{11} & \dots & X_{1n} \\ \vdots & & \vdots \\ X_{n1} & \dots & X_{nn} \end{bmatrix}.$$

In general this is a tedious computation and sometimes only estimates are possible, unless the matrix J_ψ and consequently $X(t)$ has some zeros.

Theorem 1.3.5

$$\dot{x}(t) = A(t)x \tag{1.5}$$

$$x(t_0) = x_0,$$

where $A(t) = J_\psi$ is a locally integrable $n \times n$ matrix such that $A(t+\omega) = A(t)$. let ρ_i denote the i^th Floquent multiplier. Then:

(i) All solutions $x(t)$ of (1.5) satisfy $x(t) \to 0$ as $t \to \infty$ if $|\rho_i| < 1$, $i = 1, 2, ..., n$, in which case $x = \psi(t)$ is asymptotically stable in the sense of Liapunov.

(ii) Some solution of (1.5) is a nontrivial ω-periodic solution if and only if $\rho_i = 1$ for some $i \in \{1, 2, ..., n\}$.

(iii) If however, $|\rho_j| > 1$ for some $j \in \{1, 2, ..., n\}$, then $x = \psi(t)$ is unstable.

Hopf-Andronov-Poincare Bifurcation Theorem [30]

Theorem 1.3.6 *Let*

$$\dot{x}(t) = F(x, \mu) \tag{1.6}$$

$$x(t_0) = x_0,$$

where μ is a bifurcation parameter, $x \in \Re^n, \mu \in \Re$, and $F \in C^r(\Re^n \times \Re, \Re^n)$. Suppose:

(i) $F \in C^r, r \geq 2$ on some sufficiently large open set D containing the equilibrium, $(x, \mu) = (x_0, \mu_0) = E_{\mu_0}$, where x_0 is an isolated critical point of $F(x, \mu)$.

(ii) $F(x, \mu) = 0$ for some curve $x = x(\mu)$ with $x(\mu) \in N(x_0, \mu_0)$, a neighborhood of (x_0, μ_0) on D.

(iii) The Jacobian matrix $J_\mu = D_x F(x_0, \mu_0)$ has a pair of complex conjugate eigenvalues λ and $\bar{\lambda}$ such that

$$\lambda(\mu) = \alpha(\mu) + i\beta(\mu),\ \lambda(\mu) \in C^r,$$

where

1. $\beta(\mu_0) > 0$,
2. $\alpha(\mu_0) = 0$,
3. $\frac{\partial}{\partial \mu} Re\lambda(\mu_0) = \alpha'(\mu_0) \neq 0$ *(transversality criterion) where $E_{\mu=\mu_0}$ is asymptotically stable.*

(iv) The remaining $n-2$ eigenvalues of $J_\mu = D_x F(x_0, \mu_0)$ have nonzero (preferably negative) real parts.

Then $E_{\mu=\mu_0} = (x_0, \mu_0)$ is a bifurcation point of the equilibrium, $x = x_0$, leading to a limit cycle for some small values of $\mu \neq \mu_0$. If $\mu > \mu_0$ the bifurcation is supercritical and if $\mu < \mu_0$, then the bifurcation is subcritical. If the bifurcation is all at $\mu = \mu_0$, there is a center around $x = x_0$ and infinitely many neutrally stable concentric closed(periodic) orbits surrounding $x = x_0$.

The Implicit Function Theorem [89,91]

Theorem 1.3.7 *suppose that $U \subset \Re^n \times \Re^m$ is an open set and $F : U \to \Re^m$ is a C^r function for some $r \geq 1$. Represent a point $p \in U$ by $p(x, y)$ with $x \in \Re^n$ and $y \in \Re^m$ and the coordinate functions of F by f_i, i.e. $F = (f_1, f_2, ..., f_m)$. Assume that for some $(x_0, y_0) \in U$*

$$(\frac{\partial f_i}{\partial y_j}(x_0, y_0))_{1 \leq i,j \leq m}$$

is an invertible $m \times m$ matrix. Let $C = F(x_0, y_0) \in \Re^m$. Then there is an open set V containing x_0, and an open set W containing y_0 with $V \times W \subset U$, and a C^r function $h : V \to W$ such that

$$h(x_0) = y_0, \;\; F(x, h(x)) = C, x \in V.$$

Furthermore, for each $x \in V$, $h(x)$ is the unique $y \in W$ such that $F(x, y) = C$.

The Poincaré-Bendixson Theorem [83]

Theorem 1.3.8 *Consider the system*

$$\dot{x}(t) = f(x),$$

where, $x \in \Re^2$, $f \in C^1(\Re^2, \Re^2)$.

Let M be a positively invariant region for the vector field of the system, containing a finite number of fixed points. Let $p \in M$ and consider the ω-limit set of p denoted by $\omega(p)$. Then one of the following possibilities holds:

1) $\omega(p)$ is a fixed point (critical equilibrium point).

2) $\omega(p)$ is a closed orbit.

3) $\omega(p)$ consists of a finite number of fixed points $p_1, ..., p_n$ and orbits γ with the alpha limit set and omega limit set of γ being such that $\alpha(\gamma) = p_i$ and $\omega(\gamma) = p_j$.

In particular, if M contains no fixed points, then it contains a limit cycle.

The Routh-Hurwitz Criterion [3,26]

Consider the autonomous system

$$\dot{x}(t) = F(x), \tag{1.7}$$

where $x \in \Re^n$, $F \in C(\Re^n, \Re^n)$. Let $A = DF(E(x_0))$ be the $n \times n$ matrix of linearization of the system around the fixed point $E(x_0)$, leading to the system

$$\dot{y}(t) = Ay, \; y(0) = y_0.$$

Consider the characteristic polynomial equation $p(\lambda, A) = 0$ where

$$\begin{aligned} p(\lambda, A) &= det(A - \lambda I) \\ &= \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_n. \end{aligned}$$

Define n matrices as follows

$$H_1 = a_1, \; H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, \; H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix}$$

$$H_k = \begin{bmatrix} a_1 & 1 & 0 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & \dots & 0 & \\ a_5 & a_4 & a_3 & a_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \dots & 0 \\ a_{2k-1} & a_{2k-2} & a_{2k-3} & a_{2k-4} \dots & a_k & \end{bmatrix}, \; H_n = \begin{bmatrix} a_1 & 1 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & \dots & 0 \\ \vdots & \vdots & \vdots & & \\ 0 & 0 & 0 & \dots & a_n \end{bmatrix},$$

where the (i, j) term in the matrix H_k is

1) a_{2i-j} for $0 < 2i - j < n$,

2) 1 for $2i - j = 0$,

3) 0 for $2i < j$ or $2i > n + j$.

Theorem 1.3.9 *The eigenvalues of (1.7) have negative real parts and consequently, the equilibrium $E(x_0)$ is locally asymptotically stable if and only if*

$$det(H_j) > 0, \; (j = 1, 2, ..., k).$$

In particular for $n = 2, 3, 4$ *the criteria reduce to:*

$n = 2$: $a_1 > 0$, $a_2 > 0$.

$n = 3$: $a_1 > 0$, , $a_3 > 0$, $a_1 a_2 > a_3$.

$n = 4$: $a_1 > 0$, $a_3 > 0$, $a_4 > 0$, $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$.

1.4 Outline of thesis

The thesis will consist of five chapters in total. Following this introductory chapter will be four chapters, each containing a class of models to simulate certain specific or general cancers, including tumor growth and leukemia, together with treatment by chemotherapy. The idea in modeling will be to consider cancer and healthy cells as competing populations for the bodily resources, and the chemotherapy as acting like a predator on both.

From the viewpoint of biological stoichiometry, Chapter 2 deals with vascular tumor growth and its treatment with chemotherapy techniques. Sufficient criteria are obtained for the uniform persistence of populations and the extinction of cancer cells. Conditions for the global stabilities of the cancer-free equilibrium and the interior equilibrium are obtained. Necessary and sufficient conditions for Hopf bifurcation to occur is also obtained by using the time delay as a bifurcation parameter. By so doing, we hope to identify criteria involving combinations of parameters which yield the eradication of the cancer cells or at least the existence of Hopf bifurcation with stable limit cycles or of permanence, which means in either case that the normal cells will persist at some level.

Chapter 3 utilizes a special case (logistic) of the model developed in [75] to study the cytokinetics of cancer and normal cells under chemotherapy, and extends it to the diffusion case to model the spread of cancer within a site (such as leukemia in the bone marrow). The existence, uniqueness, and boundedness of the solutions are established by means of a comparison principle and a monotonicity method. Persistence criteria for the normal cells and cancer cells are also derived. Here our results may be interpreted as to a general chemotherapeutic treatment of leukemia, with a view to identifying parametric relations for control of leukemia growth.

In chapter 4, a generalized mathematical model is proposed to give a plausible explanation of events that lead to the progression of chronic myeloid leukemia to blast

crisis. The stabilities for the complicated system with one or two delays are fully analyzed and necessary and sufficient conditions for stability switches to occur are obtained. When the system remain stable, this corresponds to preservation at some level of both cancer and healthy cells. However, when stability switches occur, this could indicate switching between remission and cancer growth.

Finally, Chapter 5 studies the cycle-specificity of chemotherapy techniques utilizing a system of delayed differential equations to take into account the phases of the cell cycle. Stabilities of cancer-free equilibria are fully analyzed and conditions for stability switching and its biological implications are given. Also, necessary and sufficient conditions for Hopf bifurcation to occur are derived by using the time delay as a bifurcation parameter. Here again, we hope to identify relations among the parameters that will lead to eradication of the cancer, or at least control on its growth.

Numerical examples are used to illustrate results throughout the thesis.

2

A Mathematical Model of Vascular Tumor Treatment by Chemotherapy

2.1 Introduction

Cancer is a multi-stage malignant disease in which certain cells proliferate with disregard to the regulatory mechanisms that act to regulate the growth of healthy cells. These cells then biotransform to stages of greater malignancy, characterized by oncogene activation/mutation, heterogeneity, invasion and metastasis [8,38,62,77]. In general, such a cellular proliferation is called neoplasia and hence cancer is sometimes referred to as a neoplastic disease. The term tumor which denotes swelling is commonly used to refer to neoplasm, while cancer is a general term for all malignant neoplasms. A malignant tumor or cancer is a configuration of neoplastic cells in an anatomic organ or tissue such that these cancer cells differ from healthy cells in histopathologic, morphologic, immunologic and cytokinetic characteristics [62,86].

Having a cancerous tumor has been widely acknowledged as one of the most deadly diseases of mankind. Studies show cancer cells not only compete with normal cells for resources, but also compete with each other and against normal cells throughout the body for the same resources, such as oxygen, nutrients, space, and so on, among which

phosphorus is one important resource that cancer and normal cells are competing for [60]. Phosphorus has been considered as an important element both structurally and functionally in all organisms. Recent works [10,14,110] show that cancer cells up-regulate ribosome synthesis, a process which requires large amounts of phosphate. Ribosomes are the structures where structural proteins are synthesized, and since proteins are the most abundant macromolecules, the ribosomes constitute the core of the biosynthesis machinery in all cells and play a significant role in tumor biology [60,105].

Biological stoichiometry is the study of the balance of energy and multiple chemical elements in biological systems [100]. The growth rate hypothesis proposes that ecologically significant variations in the relative requirements of an organism for C, N and P are determined by its mass-specific growth rate because of the heavy demand for P-rich ribosomal RNA under rapid growth [28]. Two important assumptions of the growth rate hypothesis are (1) that there is a positive relationship between rRNA concentration and specific growth rate, and (2) that the P in rRNA makes up a significant fraction of the total P in organisms [105]. Recent numerous experimental data show that P-rich animals are usually sensitive to the P-content of their foods. They will suffer strong declines in growth and reproduction when consuming food low in P, which make them vulnerable to irregular population dynamics and possible extinction in environments that do not provide them with sufficient P [100].

Biological stoichiometry and the growth rate hypothesis have strong relevance for tumor biology. The idea of modeling cancer interactions with healthy tissue from the viewpoint of biological stoichiometry and the growth rate hypothesis was first proposed by Kuang et al. [60]. However, their work only included a numerical and not an analytical analysis. It also did not include any treatment. Here we continue their work and incorporate chemotherapy treatment with the model developed in [60](see [60] for the derivation of the model) and mathematically explore the effects of treatment on such tumor growth. Current therapeutic approaches center on destroying individual cancer cells or on slowing their reproduction. While the approach may be increasingly successful for many cancers [9], they may be inherently limited in their ability to defeat many forms of cancer [42]. However, by applying a stoichiometric perspective to the modeling, which may better

reflect the multivariate material demands of populations, we might be better able to design a drug protocol in favor of the patient. It is within this context our studies of treatment for such tumor growth may be significant.

The organization of this chapter is as follows. In the next section, we develop our model. In section 2.3 we discuss the invariance of nonnegativity, boundedness of solutions, nature of equilibria, permanence and global stability in the no treatment case. In the section that follows we look at the continuous treatment case: we discuss the existence, local and nonlocal stability of relevant equilibria, and check the effects of the time delay on the stability of solutions. These are done both analytically and numerically.

2.2 The model

The model consists of three ordinary differential equations and one functional differential equation, altogether simulating the interactions between the normal cells, parenchyma (cancerous) cells, blood vessels within the tumor, and chemotherapy agents. Let $x(t)$ and $y(t)$ be the mass of healthy and cancer cells, $z(t)$ is the mass of blood vessels within the tumor (in [60] $z(t)$ was the number of blood vessels), and $u(t)$ is the mass of chemotherapy agents. Then the model is given as

$$\begin{aligned}
\dot{x}(t) &= x(t)[a\,min(1,\frac{P_e}{nk_hf}) - d_x - (a-d_x)\frac{x(t)+y(t)+z(t)}{k_h}] - \frac{p_1x(t)u(t)}{\bar{a}_1+x(t)}\\
\dot{y}(t) &= y(t)[b\,min(1,\frac{P_e}{mk_hf})min(1,L) - d_y - (b-d_y)\frac{y(t)+z(t)}{k_t}] - \frac{p_2y(t)u(t)}{\bar{a}_2+y(t)}\\
\dot{z}(t) &= cy(t-\tau) - d_zz(t) - \frac{p_3z(t)u(t)}{\bar{a}_3+z(t)}\\
\dot{u}(t) &= \Delta - [\xi + \frac{c_1x(t)}{\bar{a}_1+x(t)} + \frac{c_2y(t)}{\bar{a}_2+y(t)} + \frac{c_3z(t)}{\bar{a}_3+z(t)}]u(t)\\
L &= \frac{g(z-\alpha y)}{y},\\
P_e &= P-(nx+my+nz),
\end{aligned} \tag{2.1}$$

with initial conditions

$$x(0)=x_0>0,\ y(t)=\phi_2(\theta)\geq 0, -\tau\leq\theta\leq 0,\ z(0)=z_0\geq 0,\ u(0)=u_0\geq 0.$$

Here the chemotherapy might be the combination of several chemical agents, which acts like a predator on both healthy and cancer cells. The growth rate of heathy tissue decelerates as the masses of both the healthy and tumor tissue approache k_h. A similar situation does not apply to the tumor. The tumor growth rate is only modified by the relationship between tumor mass and tumor carrying capacity, k_t; mass of healthy tissue has no effect on the tumor. The parameters in the model can be interpreted as follows:

a, b are the maximum per capita rates at which healthy cells and tumor cells proliferate respectively in a phosphorus-rich environment.

k_h, k_t are respective carrying capacities of healthy cells and tumor cells.

d_x, d_y represent the respective constant per capita mortality of healthy cells and tumor cells,

p_i, $i = 1, 2, 3$ are the predation coefficients of u on x, y and z.

$\bar{a}_i$, $i = 1, 2, 3$ determine the rate at which x, y, z, in the absence of competition and predation, reach carrying capacities.

c_i, $i = 1, 2, 3$ represent the combination rates of the chemotherapy agent with the cells. Hence they are proportional to p_i, $i = 1, 2, 3$.

P is the homeostatically regulated total amount of phosphorus within the organ.

m represents the mean amount of phosphorus (g) per kilogram of parenchyma cells.

n is the mean amount of phosphorus per kilogram of healthy cells, including both healthy organ tissue and vascular endothelial cells within the tumor stroma.

Δ represents the continuous infusion rate of chemotherapy.

ξ is the washout rate of chemotherapy at the site.

τ represents the time it takes for vascular endothelial cells to respond to angiogenic growth factors, divide, degrade their basement membranes, migrate to the site of growth and mature into working endothelium.

α is the mass of cancer cells that one unit of blood vessel can just barely maintain.

g measures the sensitivity of tumor tissue to the lack of blood.

All constants are positive. To make this model more realistic, we impose certain inequalities among the parameters. It is well known that cancer cells grow at a much faster rate than normal cells. The chemotherapy agents must be considerably more effective in killing cancer cells than in killing normal cells in order for the treatment to be effective.

This leads to the inequality:

$$b > a, \quad p_2 >> p_1.$$

The growth rate is limited by nutrients and decreases whenever the concentration of extracellular phosphorus drops below n. The same applies to tumor cells. Therefore, our analysis throughout this chapter, is simplified by the assumption that

$$\frac{P_e}{nk_hf} < 1, \qquad L > 1. \tag{2.2}$$

Clearly (2.2) implies that

$$\frac{P_e}{mk_hf} < 1,$$

since $m > n$.

Now by substituting $P_e = P - (nx + my + nz)$ into system (2.1)with the assumption (2.2) and simplifying it, we obtain

$$\begin{aligned}
\dot{x}(t) &= x(t)[a_0 - a_1x(t) - a_2y(t) - a_3z(t)] - \frac{p_1x(t)u(t)}{\bar{a}_1 + x(t)} \\
\dot{y}(t) &= y(t)[b_0 - b_1x(t) - b_2y(t) - b_3z(t)] - \frac{p_2y(t)u(t)}{\bar{a}_2 + y(t)} \\
\dot{z}(t) &= cy(t-\tau) - d_zz(t) - \frac{p_3z(t)u(t)}{\bar{a}_3 + z(t)} \\
\dot{u}(t) &= \Delta - [\xi + \frac{c_1x(t)}{\bar{a}_1 + x(t)} + \frac{c_2y(t)}{\bar{a}_2 + y(t)} + \frac{c_3z(t)}{\bar{a}_3 + z(t)}]u(t),
\end{aligned} \tag{2.3}$$

with initial conditions

$$x(0) = x_0 > 0,\ y(t) = \phi_2(\theta) \geq 0, -\tau \leq \theta \leq 0,\ z(0) = z_0 \geq 0,\ u(0) = u_0 \geq 0,$$

where

$$a_0 = \frac{aP}{nk_hf} - d_x,\ a_1 = \frac{a}{k_hf} + \frac{a-d_x}{k_h},\ a_2 = \frac{ma}{fnk_h} + \frac{a-d_x}{k_h},\ a_3 = \frac{a}{fk_h} + \frac{a-d_x}{k_h};$$

and

$$b_0 = \frac{bP}{mk_hf} - d_y,\ b_1 = \frac{nb}{mfk_h},\ b_2 = \frac{b}{k_hf} + \frac{b-d_y}{k_t},\ b_3 = \frac{nbk_t + mfk_h(b-d_y)}{mfk_hk_t}.$$

Throughout this chapter our analysis will be based on the simplified system (2.3).

At this point we establish some important properties of system(2.3).

Lemma 2.2.1 *All solutions with positive initial values remain positive.*

Proof. By uniqueness of solutions, since $x \equiv 0$ is a solution of the first equation of (2.3), no solution with $x(t) > 0$ at any time $t \geq 0$ can become zero in finite time. Similarly, the same is true for $y(t)$. Since $\dot{u}(0) = \Delta > 0$, no solution $u(t)$ of (2.3) with $u(t) > 0$ can become zero. Using a comparison theory and induction methods, we can prove that $z(t)$ must remain positive provided that $y(t)$ is positive on $t \geq -\tau$,which it is. □

Theorem 2.2.1 *System (2.3) is dissipative.*

Proof. Since the initial conditions are nonnegative, then so are the solutions. From (2.3), we have

$$\frac{dx}{dt} \leq x(a_0 - a_1 x), \quad \frac{dy}{dt} \leq y(b_0 - b_2 y).$$

It follows from standard comparison theory that

$$\limsup_{t\to\infty} x(t) \leq a_1^{-1} a_0, \quad \limsup_{t\to\infty} y(t) \leq b_2^{-1} b_0.$$

Let T be so large that $0 \leq y(t) \leq b_0 b_2^{-1}$ for $t \geq T$. Then we have

$$\frac{dz}{dt} \leq b_2^{-1} b_0 c - d_z z,$$

which then implies, again using a comparison theorem and after some computations, that

$$\limsup_{t\to\infty} z(t) \leq d_z^{-1} b_2^{-1} b_0 c.$$

Now we have that,

$$\frac{du}{dt} \leq \Delta - \xi u$$

giving

$$\limsup_{t\to\infty} u(t) \leq \xi^{-1}\Delta.$$

Hence, the region $\Re = \{(x, y, z, u) \in R_+^4 : 0 \leq x \leq a_1^{-1} a_0,\ 0 \leq y \leq b_2^{-1} b_0,\ 0 \leq z \leq d_z^{-1} b_2^{-1} b_0 c,\ 0 \leq u \leq \xi^{-1}\Delta\}$ is an attracting invariant region proving the property. □

2.3 The no treatment case

Depending on the initial conditions, a trajectory can either converge to an attractor, or diverge to infinity. In our system the attractor may be an equilibrium, a limit cycle, or a higher dimensional subset of phase space. Knowing the conditions for which we can obtain all these possibilities enables us to better understand the long term behavior of our system that is crucial to the outcome of therapy. We first determine the type of dynamics that can arise in the system without the presence of the drug and then study the case with drugs. The rationale behind this is to use the information about the drug-free system when designing chemotherapeutic protocols. When we stop the treatment, we would like the patient to be "cured", or to be inside the basin of attraction of the cancer-free fixed points of this new drug-free system. It is also of interest to study how the delay τ affects the behavior of our system and how each element contributes to the overall stability. Here the model is modified to the form

$$\begin{aligned} \dot{x}(t) &= x(t)[a_0 - a_1 x(t) - a_2 y(t) - a_3 z(t)] \\ \dot{y}(t) &= y(t)[b_0 - b_1 x(t) - b_2 y(t) - b_3 z(t)] \\ \dot{z}(t) &= cy(t-\tau) - d_z z(t) \end{aligned} \tag{2.4}$$

with initial conditions

$$x(0) = x_0 > 0,\ y(t) = \phi_2(\theta) \geq 0, -\tau \leq \theta \leq 0,\ z(0) = z_0 \geq 0.$$

2.3.1 Asymptotic behavior and Hopf bifurcation

Equilibria

System (2.4) has a trivial equilibrium $E_0(0,0,0)$ and a one-dimensional equilibrium $E_1(\bar{x},0,0)$. The two-dimensional equilibrium is $E_2(0,\hat{y},\hat{z})$. Finally a possible interior equilibrium is $E_3(x^*,y^*,z^*)$.

By solving the algebraic equation with $y = z = 0$

$$a_0 - a_1 x(t) = 0,$$

we obtain

$$\bar{x} = a_0 a_1^{-1} = \frac{aP - nk_h f d_x}{n[a + (a - d_x)f]}.$$

Similarly, solving the algebraic system with $x = 0$

$$\begin{aligned} b_0 - b_2 y - b_3 z &= 0 \\ cy - d_z z &= 0, \end{aligned}$$

gives

$$\hat{y} = \frac{b_0}{b_2 + b_3 c d_z^{-1}} = \frac{k_t d_z (bP - m k_h f d_y)}{b k_t (m d_z + nc) + m k_h f (b - d_y)(c + d_z)}, \quad \hat{z} = \frac{c}{d_z}\hat{y}.$$

Again, by solving the system

$$\begin{aligned} a_0 - a_1 x - a_2 y - a_3 z &= 0 \\ b_0 - b_1 x - b_2 y - b_3 z &= 0 \\ cy - d_z z &= 0 \end{aligned}$$

we have

$$\begin{aligned} x^* &= \frac{a_0}{a_1} - (\frac{a_2}{a_1} + \frac{c}{d_z})y^* \\ y^* &= \frac{(a_0 b_1 - a_1 b_0) d_z}{(a_2 b_1 - a_1 b_2) d_z + (a_3 b_1 - a_1 b_3) c} \\ z^* &= \frac{c y^*}{d_z}. \end{aligned}$$

Characteristic equation

In order to determine the stability of an equilibrium $E(x, y, z)$, we linearize system (2.4) about E and obtain

$$w'(t) = Aw(t) + Bw(t - \tau),$$

where

$$w(t) = (x(t), y(t), z(t))^T$$

$$A = \begin{bmatrix} a_0 - 2a_1 x - a_2 y - a_3 z & -a_2 x & -a_3 x \\ -b_1 y & b_0 - b_1 x - 2b_2 y - b_3 z & -b_3 y \\ 0 & 0 & -d_z \end{bmatrix}$$

$$B = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & c & 0 \end{bmatrix},$$

where matrices A and B are computed at the equilibrium under consideration. The stability is determined by computing the roots of the characteristic equation

$$det(A + Be^{-\lambda\tau} - \lambda I) = 0. \tag{2.5}$$

Nonpersistence

we say a system is nonpersistent if there is solution $(x(t), y(t), z(t))$ such that $(x(0), y(0), z(0)) > 0$, then either

$\limsup_{t\to\infty} x(t) = 0$, and/or $\limsup_{t\to\infty} y(t) = 0$, and/or $\limsup_{t\to\infty} z(t) = 0$.

In particular, nonpersistence with respect to cancer means

$\limsup_{t\to\infty} y(t) = 0$, and/or $\limsup_{t\to\infty} z(t) = 0$.

Theorem 2.3.1 *Suppose the interior equilibrium $E_3(x^*, y^*, z^*)$ exists. If either or both of*

(i) $a_0 < a_2\hat{y} + a_3\hat{z}$ or

(ii) $b_0 < b_1\bar{x}$,

hold, then system (2.4) is nonpersistent for all $\tau \geq 0$, provided that $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) > cb_3\hat{z}$. Furthermore, if $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) < cb_3\hat{z}$, then system (2.4) is nonpersistent at least for small values of the time delay.

Proof. Clearly the trivial equilibrium is a hyperbolic saddle point. The characteristic equation about $E_1(\bar{x}, 0, 0)$ is given by

$$\begin{vmatrix} a_0 - 2a_1\bar{x} - \lambda & -a_2\bar{x} & -a_3\bar{x} \\ 0 & b_0 - b_1\bar{x} - \lambda & 0 \\ 0 & ce^{-\lambda\tau} & -d_z - \lambda \end{vmatrix} = 0.$$

Hence the eigenvalues are

$$\begin{aligned} \lambda_1 &= a_0 - 2a_1\bar{x} = -\frac{aP - nfk_hd_x}{nfk_h} < 0 \\ \lambda_2 &= b_0 - b_1\bar{x} = \frac{nbd_xk_h + bP(a - d_x)}{mk_h[a + (a - d_x)f]} - d_y \\ \lambda_3 &= -d_z < 0. \end{aligned}$$

In the case $b_0 < b_1\bar{x}$, all eigenvalues are negative and E_1 is asymptotically stable for all $\tau \geq 0$. Therefore, a necessary condition for the tumor growth is $b_0 > b_1\bar{x}$, i.e.

$$P > [b(a - d_x)]^{-1}[(a - d_x)mfk_hd_y + (amd_y - bnd_x)k_h].$$

Let (i) hold. Evaluating the Jacobian matrix about $E_2(0, \hat{y}, \hat{z})$, gives

$$J = \begin{bmatrix} a_0 - a_2\hat{y} - a_3\hat{z} & 0 & 0 \\ -b_1\hat{y} & b_0 - 2b_2\hat{y} - b_3\hat{z} & -b_3\hat{z} \\ 0 & ce^{-\lambda\tau} & -d_z \end{bmatrix}.$$

Hence, one of the eigenvalues is

$$\lambda = a_0 - a_2\hat{y} - a_3\hat{z},$$

which is negative by assumption. The other roots satisfy

$$\lambda^2 - (b_0 - 2b_2\hat{y} - b_3\hat{z} - d_z)\lambda - (b_0 - 2b_2\hat{y} - b_3\hat{z})d_z + cb_3\hat{z}e^{-\lambda\tau} = 0. \qquad (2.6)$$

It follows from Freedman and Rao [34] that equation (2.6) has all roots with negative real parts for $\tau \geq 0$ if $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) > cb_3\hat{z}$. On the other hand, if $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) < cb_3\hat{z}$, then E_2 is asymptotically stable for $0 \leq \tau \leq d_z(2b_2\hat{y} + b_3\hat{z} - b_0)/cb_3\hat{z}$.

Corollary 2.3.2 *Whenever E_2 is stable in the x-direction, then the interior equilibrium E_3 cannot be globally stable for system (2.4), at least for small time delays.*

Proof. It follows from *Theorem* 2.3.1 that stability of E_2 implies nonpersistence, at least for small values of delay. Hence global stability cannot hold as it implies persistence of the system under consideration.

Theorem 2.3.1 and *Corollary* 2.3.2 show that the mature time for vascular endothelial cells plays an important role in the global survival of all populations. They demonstrate that there exists a certain situation in which one of populations will lose the competition between them and is driven to death with a certain value of time delay (see *Figure* 2.1) .

Permanence

In this section we shall prove that the instability of boundary equilibria implies that system (2.4) is permanent. Thus we prove the open problem in [60]. Before starting our theorem, we give some definitions.

Let $\Omega = \{(x, y, z) \in R^3_+ : 0 \leq x \leq a_1^{-1}a_0,\ 0 \leq y \leq b_2^{-1}b_0,\ 0 \leq z \leq d_z^{-1}b_2^{-1}b_0c\}$. Then it is easy to show that Ω is an attracting invariant region for system (2.4).

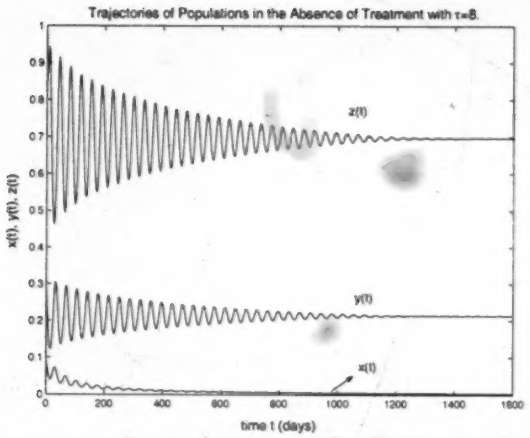

Figure 2.1: A solution for model (2.4) with $a = 3\,day^{-1}$, $p = 60\,g$, $f = 0.67, n = 10\,g/kg$, $k_h = 20\,kg$, $k_t = 10\,kg$, $b = 3.01\,day^{-1}$, $d_x = 1\,day^{-1}$, $d_y = 0.3\,day^{-1}$, $m = 20\,g/kg$, $d_z = 0.2\,day^{-1}$, $c = 0.654\,day^{-1}$. Here $E_2(0, 0.213, 0.698)$ is locally stable at least for $\tau < 8.4$. The interior equilibrium $E_3(0.002, 0.231, 0.698)$ cannot be globally stable and system (2.4) is nonpersistent at least for $\tau < 8.4$.

Definition 1. System (2.4) is said to be uniformly persistent if there is an $\eta > 0$ (independent of initial data) such that every solution $(x(t), y(t), z(t))$ with nonnegative initial conditions satisfies

$$\liminf_{t\to\infty} x(t) \geq \eta, \quad \liminf_{t\to\infty} y(t) \geq \eta, \quad \liminf_{t\to\infty} z(t) \geq \eta.$$

Definition 2. System (2.4) is said to be permanent if there exists a compact region $\Omega_0 \in int\Omega$ such that every solution of Eq.(2.4) with nonnegative initial conditions will eventually enter and remain in region Ω_0.

Clearly for a dissipative system uniform persistence is equivalent to permanence.

Theorem 2.3.3 *System (2.4) is permanent provided*

$$\frac{a_2 d_z + a_3 c}{2b_2 d_z + b_3 c} < \frac{a_0}{b_0} < \frac{2a_1}{b_1}.$$

Since we have uniform boundedness of solutions of system (2.4), we only need to show system (2.4) is uniformly persistent. It follows from $Definition$ 1 that uniform persistence means strictly positive solutions are eventually uniformly bounded away from

the boundary. To obtain persistence, two techniques have been employed: verifying that invariant sets in the boundary of the feasible region are not attractors and constructing Lyapunov-like functions. We shall analyze the boundary flow following techniques established in [47]. The basic idea of proving *Theorem* 2.3.3 is to show that all dynamics are trivial on the boundaries of R^3_+, that all equilibria are hyperbolic and acyclic, and that no equilibrium is asymptotically stable. By acyclicity we mean that equilibria which are connected to other equilibria through a chain of saddle connectors are not eventually connected to themselves (see Bulter, et al.[12] for a formal definition).

For the convenience of description, we first present the uniform persistence theory for infinite dimensional systems from [47]. Let X be a complete metric space. Suppose that X^0 is open, dense in X and $X^0 \subset X$, $X_0 \subset X$, $X_0 \cup X^0 = X$, $X_0 \cap X^0 = \emptyset$. Assume that $S(t)$ is a C^0 semigroup on X satisfying

$$S(t) : \begin{cases} X^0 \to X^0 \\ X_0 \to X_0. \end{cases} \tag{2.7}$$

Let $S_b(t) = S(t)|_{X_0}$ and let A_b be the global attractor for $S_b(t)$.

Lemma 2.3.1 *Suppose that $S(t)$ satisfies Eq.(2.7) and we have the following:*
(i) there is a $t_0 \geq 0$ such that $S(t)$ is compact for $t > t_0$,
(ii) $S(t)$ is point dissipative in X,
(iii) $\hat{A}_b = \cup_{x \in A_b} \omega(x)$ is isolated and has an acyclic covering $\hat{M}$, where $\hat{M} = \{M_1, M_2, ..., M_n\}$,
(iv) $W^s(M_i) \cap X^0 = \emptyset$ for $i = 1, 2, ..., n$.
Then X_0 is a uniform repellor with respect to X^0, i.e. there is an $\epsilon > 0$ such that for any $x \in X^0$, $\lim_{t \to \infty} \inf\, d(S(t)x, X_0) \geq \epsilon$, where d is the distance of $S(t)x$ from X_0.

Now we sketch a proof that the boundary planes of R^3_+ repel the positive solutions of system (2.4) uniformly. Let us define

$$\begin{aligned} C_1 &= \{(\phi_1, \phi_2, \phi_3) \in C([-\tau, 0], R^3_+) : \phi_1(\theta) = 0, \phi_2(\theta) = 0, \theta \in [-\tau, 0]\} \\ C_2 &= \{(\phi_1, \phi_2, \phi_3) \in C([-\tau, 0], R^3_+) : \phi_1(\theta) = 0, \phi_2(\theta)\phi_3(\theta) \neq 0, \theta \in [-\tau, 0]\} \\ C_3 &= \{(\phi_1, \phi_2, \phi_3) \in C([-\tau, 0], R^3_+) : \phi_1(\theta) \neq 0, \phi_2(\theta) = 0, \theta \in [-\tau, 0]\}. \end{aligned}$$

If $C_0 = C_1 \cup C_2 \cup C_3$ and $C^0 = intC([-\tau, 0], R^3_+)$, it suffices to show that there exists an $\epsilon_0 > 0$ such that for any solution u_t of system (2.4) initiating from C^0, $\lim_{t\to+\infty} \inf d(u_t, C_0) \geq \epsilon_0$. To this end, we verify below that the conditions of *Lemma* 2.3.1 are satisfied. It is easy to see that C^0 and C_0 are positively invariant. Moreover, conditions (i) and (ii) of *Lemma* 2.3.1 are clearly satisfied. Thus, we only need to verify conditions (iii) and (iv). There are three constant solutions E_0, E_1 and E_2 in C_0, corresponding, respectively, to $x(t) = y(t) = z(t) = 0$; $x = \bar{x}, y(t) = z(t) = 0$; and $x(t) = 0, y(t) = \hat{y}, z(t) = \hat{z}(t)$.

In the following we shall show that if invariant sets E_0, E_1 and E_2 are isolated, then $\{E_0, E_1, E_2\}$ is isolated and is an acyclic covering. To do this, we need to prove that any solution of system (2.4) initiating from C_i will remain in C_i, $i = 1, 2, 3$, which is easily shown. It is obvious that E_0 is isolated invariant. The proof of isolated invariance of E_1 and E_2 will follow easily.

We show that $W^s(E_i) \cap C^0 = \emptyset$, $i = 0, 1, 2$. Taking the case of $i = 1$ as an example to show the method, we assume the contrary, i.e. $W^s(E_1) \cap C^0 \neq \emptyset$. Then there exists a positive solution $(x(t), y(t), z(t))$ of system (2.4) such that

$$(x(t), y(t), z(t)) \to (\frac{a_0}{a_1}, 0, 0), \quad as \quad t \to +\infty.$$

Let $t_0 > 0$ be sufficiently large such that

$$\frac{a_0}{a_1} - \epsilon_0 < x(t) < \frac{a_0}{a_1} + \epsilon_0,$$

$$-\epsilon_0 < z(t) < \epsilon_0, \quad for\ t > t_0,$$

where $\epsilon_0 > 0$ is sufficiently small. Then

$$\frac{dy(t)}{dt} > y[b_0 - b_1(\frac{a_0}{a_1} + \epsilon_0) - b_2 y - b_3\epsilon_0].$$

Hence, we have

$$\liminf_{t\to+\infty} y(t) \geq \frac{b_0 b_1}{a_1 b_2}[\frac{a_1}{b_1} - \frac{a_0}{b_0} - (\frac{b_1 + b_3}{b_0 b_1})\epsilon_0] > 0,$$

which contradicts $\lim_{t\to+\infty} y(t) = 0$. Hence, $W^s(E_1) \cap C^0 = \emptyset$. Therefore, we are able to conclude from *Lemma* 2.3.1 that C_0 repels the positive solutions of system (2.4) uniformly, and hence the conclusion of *Theorem* 2.3.3 follows.

Theorem 2.3.3 obtains a sufficient condition that guarantees the global survival of all populations in the long-time period.

Global stability

Here we consider the problem of global stability of the interior equilibrium E_3 defined in the previous section. We use ideas similar to Shukla [95]. However we note that his proof is incomplete as he did not establish the boundedness of the solutions. For an arbitrary solution of (2.4) we define a positive definite function V by

$$\begin{aligned} V(x(t),y(t),z(t)) &= x(t)-x^*-x^*\ln(x(t)/x^*) \\ &\quad +\alpha[y(t)-y^*-y^*\ln(y(t)/y^*)] \\ &\quad +\frac{1}{2}\alpha b_2\int_{-\tau}^{0}[y(t+s)-y^*]^2ds \\ &\quad +\frac{1}{2}(z(t)-z^*)^2, \end{aligned} \tag{2.8}$$

where α are positive constants to be determined later.

After some algebraic manipulations we obtain that the time derivative of V along the

solutions of (2.4) is given by

$$\begin{aligned}
\dot{V} &= (x-x^*)\frac{\dot{x}(t)}{x(t)} + \alpha(y-y^*)\frac{\dot{y}(t)}{y(t)} + (z-z^*)\dot{z}(t) + \frac{1}{2}b_2\alpha[(y-y^*)^2 - (y(t-\tau)-y^*)^2] \\
&= (x-x^*)(a_0 - a_1x - a_2y - a_3z) + \alpha(y-y^*)(b_0 - b_1x - b_2y - b_3z) \\
&\quad +(z-z^*)(cy(t-\tau) - d_zz) + \frac{1}{2}b_2\alpha[(y-y^*)^2 - (y(t-\tau)-y^*)^2] \\
&= (x-x^*)[-a_1(x-x^*) - a_2(y-y^*) - a_3(z-z^*)] + \alpha(y-y^*)[-b_1(x-x^*) \\
&\quad -b_2(y-y^*) - b_3(z-z^*)] + (z-z^*)[c(y(t-\tau)-y^*) - d_z(z-z^*)] \\
&\quad -\frac{1}{2}b_2\alpha[(y-y^*)^2 - (y(t-\tau)-y^*)^2] \\
&= -a_1(x-x^*)^2 - \frac{1}{2}b_2\alpha(y-y^*)^2 - \frac{1}{2}d_z(z-z^*)^2 - \frac{1}{2}(b_2\alpha - c^2d_z^{-1})(y(t-\tau)-y^*)^2 \\
&\quad -\frac{1}{2}d_z[(z-z^*) - cd_z^{-1}(y(t-\tau)-y^*)]^2 \\
&\quad -\{(a_2+b_1\alpha)(x-x^*)(y-y^*) + b_3\alpha(y-y^*)(z-z^*) + a_3(z-z^*)(x-x^*)\} \\
&= -\{\frac{1}{2}a_1(x-x^*)^2 + (a_2+b_1\alpha)(x-x^*)(y-y^*) + \frac{1}{4}b_2\alpha(y-y^*)^2\} \\
&\quad -\{\frac{1}{4}b_2\alpha(y-y^*)^2 + b_3\alpha(y-y^*)(z-z^*) + \frac{1}{4}d_z(z-z^*)^2\} \\
&\quad -\{\frac{1}{4}d_z(z-z^*)^2 + a_3(z-z^*)(x-x^*) + \frac{1}{2}a_1(x-x^*)^2\} \\
&\quad -\frac{1}{2}(b_2\alpha - c^2d_z^{-1})(y(t-\tau)-y^*)^2 - \frac{1}{2}d_z[(z-z^*) - cd_z^{-1}(y(t-\tau)-y^*)]^2.
\end{aligned}$$

Clearly, if

$$\begin{aligned}
2(a_2+b_1\alpha)^2 &< a_1b_2\alpha \\
4b_3^2\alpha &< b_2d_z \\
c^2 &< b_2d_z\alpha \\
2a_3^2 &< a_1d_z. \qquad (2.9)
\end{aligned}$$

Then $\dot{V} < 0$, which leads to the following theorem.

Theorem 2.3.4 *If we choose positive α such that (2.9) holds, then the interior equilibrium $E_3(x^*, y^*, z^*)$ for system (2.4) is globally asymptotically stable.*

Theorem 2.3.4 shows that if the condition (2.9) is satisfied, the interior equilibrium $E_3(x^*, y^*, z^*)$ will be globally asymptotically stable and solutions will be eventually attracted to the interior equilibrium E_3, which means the global survival of all populations (see *Figure* 2.2).

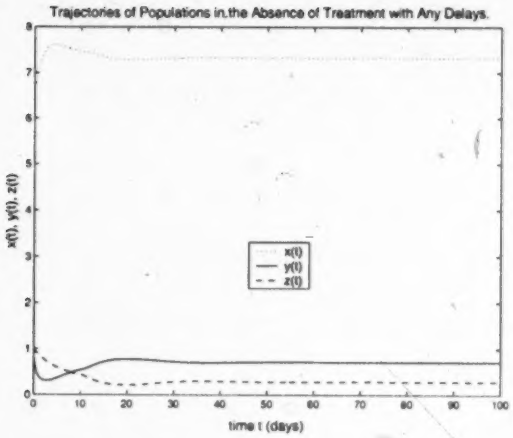

Figure 2.2: A solution for model (2.4) with $a = 3\,day^{-1}, p = 150\,g, f = 0.67, n = 10\,g/kg, k_h = 10\,kg, k_t = 3\,kg, b = 6\,day^{-1}, d_x = d_y = 1\,day^{-1}, m = 20\,g/kg, d_z = 0.2\,day^{-1}, c = 0.08\,day^{-1}$. Here $E_1(8.825, 0, 0)$ and $E_2(0, 1.677, 0.671)$ are unstable. System (2.4) is permanent and the interior equilibrium $E_3(7.342, 0.714, 0.286)$ is globally asymptotically stable, independent of the delay.

Stability and Hopf bifurcation

As shown in the previous section a stable boundary equilibrium implies $E_3(x^*, y^*, z^*)$ cannot be globally stable, at least for small τ and that the system is nonpersistent for such a delay. Thus it is of interest to know if E_3 can be locally stable. We now address ourselves to this question.

Computing the characteristic polynomial (2.5) about E_3, we obtain

$$H(\lambda) =: P(\lambda) + Q(\lambda)e^{-\lambda\tau} = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0, \qquad (2.10)$$

where

$$p_1 = (a_0 - 2a_1x^* - a_2y^* - a_1z^*)(b_0 - b_1x^* - 2b_2y^* - b_3z^*) - d_z(d_z - p_2) - a_2b_1x^*y^*$$

$$\begin{aligned} p_2 &= d_z - a_0 - b_0 + (2a_1 + b_1)x^* + (a_2 + 2b_2)y^* + (a_1 + b_3)z^* \\ p_0 &= d_z(p_1 + d_z(d_z - p_2)) \\ q_1 &= cb - 3y^* \\ q_0 &= -c(a_1b_1 + a_2b_3)x^*y^*. \end{aligned} \tag{2.11}$$

Note that when the delay $\tau = 0$, equation (2.10) becomes

$$\lambda^3 + p_2\lambda^2 + (p_1 + q_1)\lambda + p_0 + q_0 = 0. \tag{2.12}$$

By the Routh-Hurwitz criteria, necessary and sufficient conditions for solutions λ to have negative real parts are

$$p_0 + q_0 > 0,\ p_1 + q_1 > 0,\ p_2(p_1 + q_1) > p_0 + q_0. \tag{2.13}$$

When $\tau \neq 0$, there are many ways in which we can determine if there is a root of the characteristic equation (2.10) with a positive real part. Geometric arguments can be used to establish the stability of an equilibrium, such as those used by Mahaffy in [66], where the argument principle is used to count the number of zeroes of the characteristic equation (2.10) on the right hand side of the complex plane. However, in this case we will resort to some results by Cooke and van den Driessche in *Theorem* 1 of [18].

They define the function

$$F(y) = |P(iy)|^2 - |Q(iy)|^2,$$

and analyze the function $F(y)$, giving conditions under which equation (2.10) is stable as a function of τ. They also gives conditions under which stability changes may occur as the delay τ is increased and show that in these cases the equilibrium is unstable for large enough τ. In short, they showed: (a) suppose that if $F(y) = 0$ has no positive roots, then if (2.10) is stable at $\tau = 0$ it remans stable for all $\tau \geq 0$, whereas if it is unstable at $\tau = 0$ it remains unstable for all $\tau \geq 0$, (b) if $F(y) = 0$ has at least one positive root and each positive root is simple, then as τ increases, stability switches may occur, and there exists a positive $\bar{\tau}$ such that (2.10) is unstable for all $\tau > \bar{\tau}$, and as τ varies from 0 to $\bar{\tau}$, at most a finite number of stability switches may occur.

Following the steps in this theorem it is straightforward to check the stability of the equilibrium and find conditions for cancer growth. In this case $F(y)$ is found to be

$$F(y) = y^6 + m_2 y^4 + m_1 y^2 + m_0,$$

where

$$m_2 = {p_2}^2 - 2p_1, \quad m_1 = {p_1}^2 - 2p_0p_1 - {q_1}^2, \quad m_0 = {p_0}^2 - {q_0}^2.$$

Let $y^2 = x$. Then $F(y)$ becomes

$$F_1(x) = x^3 + m_2x^2 + m_1x + m_0. \tag{2.14}$$

Now we will employ a lemma from [54] which we state here.

Lemma 2.3.2 *Define*

$$\gamma = \frac{4}{27}{m_1}^3 - \frac{1}{27}{m_2}^2{m_1}^2 + \frac{4}{27}{m_2}^3m_0 - \frac{2}{3}m_2m_1m_0 + {m_0}^2.$$

Suppose that $m_0 > 0$. Then:

(I) necessary and sufficient conditions for cubic equation (2.14) to have at least one simple positive root for x are:

(i)either (a) $m_2 < 0$, $m_1 \geq 0$ and ${m_2}^2 > 3m_1$, or (b) $m_1 < 0$

and

(ii) $\gamma < 0$;

(II) necessary and sufficient conditions for cubic equations (2.14) to have no positive real roots for x are either of the following.

(i) $3m_1 > {m_2}^2$

(ii) $3m_1 = {m_2}^2$

(iii) ${m_2}^2 > 3m_1$ and $\gamma > 0$

or

(iv) ${m_2}^2 > 3m_1$ and $\gamma \leq 0, m_2 > 0$ and $m_1 > 0$.

Based on *Lemma* 1 and *Lemma* 2 and methods in [18], we obtain the following stability theorems.

Theorem 2.3.5 *Suppose that* $m_2{}^2 > 3m_1$, $\gamma \leq 0$, $m_2 > 0$ *and* $m_1 > 0$. *Then*

1) if $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the stability of equilibrium* E_3 *is independent of delay* τ *and it remains stable for all* $\tau \geq 0$,

2) if $p_0 + q_0 \leq 0$, *or* $p_1 + q_1 \leq 0$, *or* $p_2(p_1 + q_1) \leq p_0 + q_0$ *the stability of equilibrium* E_3 *does not depend on* τ *and it remains unstable for all* $\tau \geq 0$.

Theorem 2.3.6 *Suppose that* $m_2{}^2 > 3m_1$, $\gamma \geq 0$. *Then*

1) if (2.13) *holds, the stability of equilibrium* E_3 *is independent of delay* τ *and it remains stable for all* $\tau \geq 0$,

2) if (2.13) *does not hold,* E_3 *remains unstable for all* $\tau \geq 0$.

Theorem 2.3.7 *Assume that either (a)* $m_2 < 0$, $m_1 \geq 0$ *and* $m_2{}^2 > 3m_1$, *or (b)* $m_1 < 0$ *and* $\gamma < 0$. *Then there exists a positive* $\bar{\tau}$ *such that*

1) if $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the equilibrium* E_3 *remains stable for* $0 \leq \tau \leq \bar{\tau}$, *and becomes unstable for all* $\tau \geq \bar{\tau}$,

2) if $p_0 + q_0 \leq 0$, *or* $p_1 + q_1 \leq 0$, *or* $p_2(p_1 + q_1) \leq p_0 + q_0$, *the equilibrium* E_3 *remains unstable for all* $\tau \geq \bar{\tau}$. *As* τ *varies from* 0 *to* $\bar{\tau}$, *at most a finite number of stability switches may occur.*

In cancer chemotherapy, stability switching is a very important issue in the design of a drug protocol. We must keep in mind that in many cases the drugs can prevent vascular endothelial precursor cells from continuing through their immigration, maturation into vascular endothelia cells, thus trapping them at some points, where the cells die from natural causes. This effect can be interpreted as an increase in the delay τ. But as we have seen here this trapping may have an adverse effects since it may cause a fixed point to become unstable when it was stable initially (*Theorem* 2.3.7). On the other hand, the same properties can be used to the clinicians advantage, if we are certain that our parameters are in the stability switching region and the equilibrium is unstable. In this case, it may be possible to use the same trapping mechanism to stabilize the cancer-free equilibrium.

Theorem 2.3.5-2.3.7 show that there exist stability switches for the interior equilibrium by taking the time delay a variable parameter, in which a small delay makes the equilibrium

stable and the populations grow periodically at the critical value of the time delay (see *Figure* 2.3-2.5).

Now by applying *Theorem* 1 in [18], it is also straightforward to check for possible Hopf bifurcations when we increase the delay τ. The importance of Hopf bifurcations in this context is that at the bifurcation point a limit cycle is formed around the fixed point, thus resulting in stable periodic solutions. The existence of periodic solutions is of significance in cancer models because it implies that the cancer levels may oscillate around a fixed point even in the absence of any treatment. Such a phenomenon has been observed clinically and is known as "Jeff's Phenomenon" [54]. In this section, we will prove that such a Hopf bifurcation can occur. Here we are interested in the bifurcation of the coexistence of three populations. Hence we consider the characteristic equation (2.10) and rewrite it as

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0. \tag{2.15}$$

Let $\lambda = u + iv\,(u, v \in R)$ and rewrite (2.15) in terms of its real and imaginary parts as

$$\begin{aligned} u^3 - 3uv^2 + p_2(u^2 - v^2) + p_1u + p_0 &= e^{-u\tau}[q_1v\sin(v\tau) + (q_1u + q_0)\cos(v\tau)] \\ 3u^2v - v^3 + 2p_2uv + p_1v &= e^{-u\tau}[(q_1u + q_0)\sin(v\tau) - q_1v\cos(v\tau)]. \end{aligned} \tag{2.16}$$

Let $\bar{\tau}$ be such that $u(\bar{\tau}) = 0$. Then the above equations reduce to

$$\begin{aligned} p_2\bar{v}^2 - p_0 &= q_1\bar{v}\sin(\bar{v}\bar{\tau}) + q_0\cos(\bar{v}\bar{\tau}) \\ -\bar{v}^3 + p_1\bar{v} &= q_0\sin(\bar{v}\bar{\tau}) - q_1\bar{v}\cos(\bar{v}\bar{\tau}). \end{aligned} \tag{2.17}$$

It follows by taking the sum of squares that

$$\bar{v}^6 + ({p_2}^2 - 2p_1)\bar{v}^4 + ({p_1}^2 - 2p_0p_2 - {q_1}^2)\bar{v}^2 + {p_0}^2 - {q_0}^2 = 0. \tag{2.18}$$

Suppose that $\bar{v}_1$ is the last positive simple root of equation (2.18). We now show that with this value of $\bar{v}_1$ there is a $\bar{\tau}_1$ such that $u(\bar{\tau}_1) = 0$ and $v(\bar{\tau}_1) = \bar{v}_1$. Given $\bar{v}_1$, equation (2.17) can be written as

$$\begin{aligned} A\cos(\bar{\tau}_1\bar{v}_1) + B\sin(\bar{\tau}_1\bar{v}_1) &= C \\ A\sin(\bar{\tau}_1\bar{v}_1) - B\cos(\bar{\tau}_1\bar{v}_1) &= D, \end{aligned} \tag{2.19}$$

where $C^2 + D^2 = A^2 + B^2 = G^2$, say, where $G > 0$. The equations

$$A = G\cos\alpha$$
$$B = G\sin\alpha \tag{2.20}$$

determine a unique $\alpha \in [0, 2\pi]$. With this value of α, we have

$$G\cos(\bar{\tau}_1\bar{v}_1)\cos\alpha + G\sin(\bar{\tau}_1\bar{v}_1)\sin\alpha = C$$
$$G\sin(\bar{\tau}_1\bar{v}_1)\cos\alpha - G\cos(\bar{\tau}_1\bar{v}_1)\sin\alpha = D. \tag{2.21}$$

Hence

$$G\cos(\bar{\tau}_1\bar{v}_1 - \alpha) = C,\ G\sin(\bar{\tau}_1\bar{v}_1 - \alpha) = D. \tag{2.22}$$

These equations determine $\bar{\tau}_1\bar{v}_1 - \alpha$ uniquely in $[\alpha/\bar{v}_1, (\alpha + 2\pi)/\bar{v}_1]$. To apply the Hopf bifurcation theorem as stated in Marsden & McCracken [68] we state and prove the following theorem.

Theorem 2.3.8 *Suppose that equation (2.18) has at least one simple positive root and $\bar{v}_1$ is the last such root. Then $iv(\bar{\tau}_1) = i\bar{v}_1$ is a simple root of equation (2.15) and $u(\tau) + iv(\tau)$ is differentiable with respect to τ in a neighborhood of $\tau = \bar{\tau}_1$.*

Proof. To show that $iv(\bar{\tau}_1) = i\bar{v}_1$ is a simple root, we investigate equation (2.15)

$$H(\lambda) = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0.$$

Any double root λ satisfies

$$H(\lambda) = 0,\ \dot{H}(\lambda) = 0,$$

where

$$\dot{H}(\lambda) = 3\lambda^2 + 2p_2\lambda + p_1 + (q_1 - \tau q_1\lambda - \tau q_0)e^{-\lambda\tau}. \tag{2.23}$$

Substituting $\lambda = i\bar{v}_1$ and $\tau = \bar{\tau}_1$ into (2.15),(2.23) and equating real and imaginary parts if $i\bar{v}_1$ is a double root, we obtain

$$p_2\bar{v}_1^2 - p_0 = q_1\bar{v}_1\sin(\bar{v}_1\bar{\tau}_1) + q_0\cos(\bar{v}_1\bar{\tau}_1)$$
$$p_1\bar{v}_1 - \bar{v}_1^3 = -q_1\bar{v}_1\cos(\bar{v}_1\bar{\tau}_1) + q_0\sin(\bar{v}_1\bar{\tau}_1) \tag{2.24}$$

and

$$\begin{aligned} 3\bar{v}_1^2 - p_1 &= (q_1 - \bar{\tau}_1 q_0)\cos(\bar{v}_1\bar{\tau}_1) + \bar{v}_1\bar{\tau}_1 q_1 \sin(\bar{v}_1\bar{\tau}_1) \\ 2p_2\bar{v}_1 &= (q_1 - \bar{\tau}_1 q_0)\sin(\bar{v}_1\bar{\tau}) + \bar{v}_1\bar{\tau}_1 q_1 \cos(\bar{v}_1\bar{\tau}_1). \end{aligned} \tag{2.25}$$

Now, equation (2.17) can be written as $h(\bar{v}_1) = 0$, where

$$h(v) = (p_2 v^2 - p_0)^2 + (p_1 v - v^3)^2 - q_1^2 v^2 - {q_0}^2 \tag{2.26}$$

$$\dot{h}(v) = 2(p_1 v^2 - p_0)2p_2 v + 2(p_1 v - v^3)(p_1 - 3v^2) - 2v{q_1}^2. \tag{2.27}$$

By substituting (2.24) and (2.25) into (2.26), (2.27), we obtain

$$h(\bar{v}_1) = \dot{h}(\bar{v}_1) = 0.$$

It follows that $\bar{v}_1$ is a double root of equation(2.26) and that $h(\bar{v}_1) = \dot{h}(\bar{v}_1) = 0$, which is a contradiction since we have assumed that $\bar{v}_1$ is a simple root of (2.18). Hence $i\bar{v}_1$ is a simple root of equation (2.15), which is an analytic equation. By using the analytic version of the implicit function theorem(Chow & Hale [16]), we can see that $u(\tau)+iv(\tau)$ is defined and analytic in a neighborhood of $\tau = \bar{\tau}_1$. The proof is complete! □

Next, to establish Hopf bifurcation at $\tau = \bar{\tau}_1$, we need to verify the transversality condition

$$\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} \neq 0.$$

By differentiating equations (2.16) with respect to τ and setting $u = 0$ and $v = \bar{v}_1$, we obtain

$$\begin{aligned} A_1\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} - B_1\frac{dv}{d\tau}|_{\tau=\bar{\tau}_1} &= p_0\bar{v}_1\sin(\bar{v}_1\bar{\tau}_1) - p_1\bar{v}_1^2\cos(\bar{v}_1\bar{\tau}_1) \\ B_1\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} + A_1\frac{dv}{d\tau}|_{\tau=\bar{\tau}_1} &= p_1\bar{v}_1^2\sin(\bar{v}_1\bar{\tau}_1) + p_0\bar{v}_1\cos(\bar{v}_1\bar{\tau}_1)], \end{aligned} \tag{2.28}$$

where

$$\begin{aligned} A_1 &= p_1 - 3\bar{v}_1^2 + \bar{\tau}_1[q_1\cos(\bar{v}_1\bar{\tau}_1) - q_1\bar{v}_1\sin(\bar{v}_1\bar{\tau}_1) - q_0\cos(\bar{v}_1\bar{\tau}_1)] \\ B_1 &= 2p_2\bar{v}_1 + \bar{\tau}_1[q_0\sin(\bar{v}_1\bar{\tau}_1) - q_1\bar{v}_1\cos(\bar{v}_1\bar{\tau}_1) - q_1\sin(\bar{v}_1\bar{\tau}_1)]. \end{aligned} \tag{2.29}$$

Solving for $\frac{du}{d\tau}$, $\frac{dv}{d\tau}$ from (2.28) with the help of (2.17), we have

$$\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} = \frac{\bar{v}_1^2[3\bar{v}_1^4 + 2({p_2}^2 - 2p_1)\bar{v}_1^2 + {p_1}^2 - 2p_2p_0 - {q_1}^2]}{{A_1}^2 + {B_1}^2}. \tag{2.30}$$

Let $z = \bar{v}_1^2$. Then equation (2.18) reduces to

$$\Phi(z) = z^3 + ({p_2}^2 - 2p_1)z^2 + ({p_1}^2 - 2p_2p_0 - {q_1}^2)z + {p_0}^2 - {q_0}^2.$$

Hence

$$\frac{d\Phi}{dz} = 3z^2 + 2({p_2}^2 - 2p_1)z + {p_1}^2 - 2p_2p_0 - {q_1}^2.$$

As $\bar{v}_1^2$ is the last positive single root of equation(2.18), then

$$\frac{d\Phi}{dz}|_{z=\bar{v}_1^2} > 0.$$

Therefore,

$$\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} = \frac{\bar{v}_1^2}{{A_1}^2 + {B_1}^2}\frac{d\Phi}{dz}|_{z=\bar{v}_1^2} > 0.$$

We summarize the preceding details in the following theorem.

Theorem 2.3.9 *Suppose that (2.18) has at least one simple positive root and $\bar{v}_1$ is the last such root. Then a Hopf bifurcation occurs as τ passes through $\bar{\tau}_1$. On the other hand if (2.18) has no positive real roots then the interior equilibrium E^* is locally asymptotically sable for all values of τ if (2.13) holds.*

2.4 The continuous treatment case

Here we consider the full model (2.3). Again equilibria are derived and listed. We study the local stability of some relevant equilibria by analytical and numerical methods.

2.4.1 Equilibria

In this case, we denote the equilibria by variations on F and again some of them are physiologically non-feasible. As in the no treatment case, the trivial equilibrium $F_0(0, 0, 0, \xi^{-1}\Delta)$ always exists. The following equilibria may or may not exist:

$$F_1(\bar{x}, 0, 0, \bar{u}), \quad F_2(0, \hat{y}, \hat{z}, \hat{u}), \quad F_3(x^*, y^*, z^*, u^*).$$

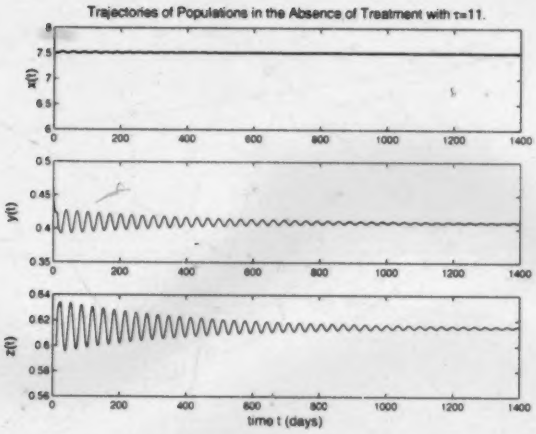

Figure 2.3: A solution for model (2.4) with $a = 3\,day^{-1}, p = 150\,g, f = 0.67, n = 10\,g/kg, k_h = 10\,kg, k_t = 3\,kg, b = 6\,day^{-1}, d_x = d_y = 1\,day^{-1}, m = 20\,g/kg, d_z = 0.2\,day^{-1}, c = 0.3\,day^{-1}$. Here the interior equilibrium $E_3(7.679, 0.397, 0.5955)$ is locally stable when the delay $\tau < 12.14$.

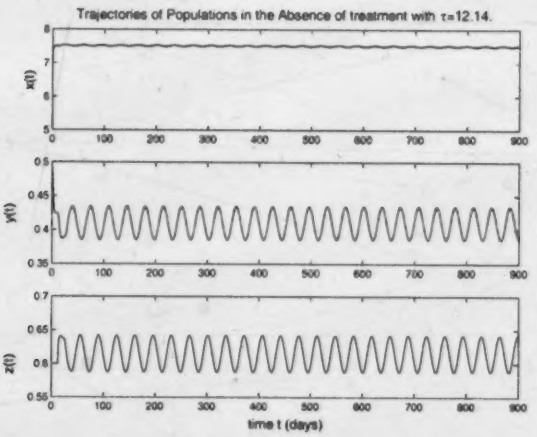

Figure 2.4: A solution for model (2.4) with $a = 3\,day^{-1}, p = 40\,g, f = 0.67, n = 10\,g/kg, k_h = 10\,kg, k_t = 5\,kg, b = 4\,day^{-1}, d_x = d_y = 1\,day^{-1}, m = 15\,g/kg, d_z = 0.2\,day^{-1}, c = 0.3\,day^{-1}$. Here the interior equilibrium $E_3(1.027, 0.068, 0.102)$ bifurcates at $\tau = 12.14$ and periodic solutions occur.

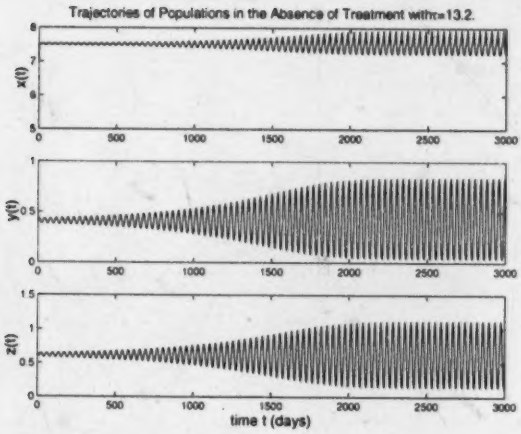

Figure 2.5: A solution for model (2.4) with $a = 3\,day^{-1}, p = 150\,g, f = 0.67, n = 10\,g/kg, k_h = 10\,kg, k_t = 3\,kg, b = 6\,day^{-1}, d_x = d_y = 1\,day^{-1}, m = 20\,g/kg, d_z = 0.2\,day^{-1}, c = 0.3\,day^{-1}$. Here the interior equilibrium $E_3(7.679, 0.397, 0.5955)$ becomes unstable but approaches to the periodic solutions when $\tau > 12.14$.

Here the symbols that are the same as in the no treatment case may have different values.

The equilibrium F_1 exists provided that the algebraic system

$$\begin{aligned} a_0 - a_1 x - \frac{p_1 u}{\bar{a}_1 + x} &= 0 \\ \Delta - [\xi + \frac{c_1 x}{\bar{a}_1 + x}]u &= 0 \end{aligned} \tag{2.31}$$

has a positive solution. System(2.31) has a positive solution provided that the quadratic equation

$$a_1(\xi + c_1)x^2 + (a_1\bar{a}_1\xi - a_0\xi - a_0c_1)x + p_1\Delta - a_0\bar{a}_1\xi = 0 \tag{2.32}$$

has a positive solution. Here a_0, a_1 are defined in the previous section. If

$$p_1\Delta < a_0\bar{a}_1\xi, \tag{2.33}$$

then equation (2.32) has a unique positive solution. Necessary and sufficient conditions for (2.32) to have two positive solutions are

$$\begin{aligned} a_1\bar{a}_1\xi &< a_0(\xi + c_1) \\ a_0\bar{a}_1\xi < p_1\Delta &< \frac{(a_1\bar{a}_1\xi - a_0\xi - a_0c_1)^2}{4a_1(\xi + c_1)}. \end{aligned} \tag{2.34}$$

From the above, we have proved the following lemma.

Lemma 2.4.1 *If (2.33) holds, then F_1 exists uniquely. If (2.34) holds, then there exist two distinct equilibria of type F_1.*

Although the other equilibria F_2 and F_3 may exist, sufficient conditions for their existence are not easily obtained. In section 2.4.3, we will present some numerical examples to illustrate cases when these equilibria exist.

2.4.2 Local stability

Here the Jacobian matrix around a general equilibrium $F(x, y, z, u)$ is

$$M = \begin{bmatrix} a_{11} & -a_2 x & -a_3 x & -\frac{p_1 x}{\bar{a}_1+x} \\ -b_1 y & a_{22} & -b_3 y & -\frac{p_2 y}{\bar{a}_2+y} \\ 0 & e^{-\lambda\tau} & -d_z & -\frac{p_3 z}{\bar{a}_3+z} \\ -\frac{\bar{a}_1 c_1 u}{(\bar{a}_1+x)^2} & -\frac{\bar{a}_2 c_2 u}{(\bar{a}_2+y)^2} & -\frac{\bar{a}_3 c_3 u}{(\bar{a}_3+z)^2} & a_{33} \end{bmatrix},$$

where

$$\begin{aligned} a_{11} &= a_0 - 2a_1 x - a_2 y - a_3 z - \frac{p_1 \bar{a}_1 u}{(\bar{a}_1 + x)^2} \\ a_{22} &= b_0 - b_1 x - 2b_2 y - b_3 z - \frac{p_2 \bar{a}_2 u}{(\bar{a}_2 + y)^2} \\ a_{33} &= -(\xi + \frac{c_1 x}{\bar{a}_1 + x} + \frac{c_2 y}{\bar{a}_2 + y} + \frac{c_3 z}{\bar{a}_3 + z}). \end{aligned}$$

Analysis of F_0

It is quite easy to get the eigenvalues associated with the trivial equilibrium F_0 which are

$$\begin{aligned} \lambda_1^{(0)} &= a_0 > 0 \\ \lambda_2^{(0)} &= b_0 > 0 \\ \lambda_3^{(0)} &= -d_z < 0 \\ \lambda_4^{(0)} &= -\xi < 0. \end{aligned}$$

Hence F_0 is a hyperbolic saddle point.

Analysis of F_1

In this case, the Jacobian matrix is given by

$$M_1 = \begin{bmatrix} a_0 - 2a_1\bar{x} - \frac{p_1\bar{a}_1\bar{u}}{(\bar{a}_1+\bar{x})^2} & -a_2\bar{x} & -a_3\bar{x} & -\frac{p_1\bar{x}}{\bar{a}_1+\bar{x}} \\ 0 & b_0 - b_1\bar{x} & 0 & 0 \\ 0 & e^{-\lambda\tau} & -d_z & 0 \\ -\frac{\bar{a}_1c_1\bar{u}}{(\bar{a}_1+\bar{x})^2} & -\bar{a}_2^{-1}c_2\bar{u} & -\bar{a}_3^{-1}c_3\bar{u} & -(\xi + \frac{c_1\bar{x}}{\bar{a}_1+\bar{x}}) \end{bmatrix}.$$

Hence two of the eigenvalues are

$$\lambda_2^{(1)} = b_0 - b_1\bar{x}, \quad \lambda_3^{(1)} = -d_z.$$

The other eigenvalues satisfy

$$\sigma(A) = \{\lambda_i^{(1)} | \lambda^2 - Tr(A)\lambda + det(A) = 0, \ i = 1, 4\},$$

where

$$A = \begin{bmatrix} a_0 - 2a_1\bar{x} - \frac{p_1\bar{a}_1\bar{u}}{(\bar{a}_1+\bar{x})^2} & -\frac{p_1\bar{x}}{\bar{a}_1+\bar{x}} \\ -\frac{\bar{a}_1c_1\bar{u}}{(\bar{a}_1+\bar{x})^2} & -(\xi + \frac{c_1\bar{x}}{\bar{a}_1+\bar{x}}) \end{bmatrix}.$$

By the Routh-Hurwitz criteria [19], if $Tr(A) < 0$ and $det(A) > 0$, then the eigenvalues of A have negative real parts. If $\bar{x} > a_0/2a_1$, then

$$\begin{aligned} Tr(A) &= a_0 - 2a_1\bar{x} - [\frac{p_1\bar{a}_1\bar{u}}{(\bar{a}_1+\bar{x})^2} + \xi + \frac{c_1\bar{x}}{\bar{a}_1+\bar{x}}] < 0 \\ det(A) &= \frac{p_1\bar{a}_1\xi\bar{x}}{(\bar{a}_1+\bar{x})^2} + (2a_1\bar{x} - a_0)(\xi + \frac{c_1\bar{x}}{\bar{a}_1+\bar{x}}) > 0. \end{aligned}$$

As a result, we have the following lemma.

Lemma 2.4.2 *If $\bar{x} > a_0/2a_1$, then the real parts of eigenvalues $\lambda_1^{(1)}$ and $\lambda_4^{(1)}$ are negative.*

Based on *Lemma* 2.4.2, we obtain the following theorem.

Theorem 2.4.1 *Suppose that $\bar{x} > a_0/2a_1$ and $b_0 \neq b_1\bar{x}$. If $b_0 > b_1\bar{x}$, then F_1 is a hyperbolic saddle point. On the other hand, if $b_0 < b_1\bar{x}$, then F_1 is asymptotically stable.*

Analysis of F_2

In this case, the Jacobian matrix is given by

$$M_2 = \begin{bmatrix} M_{11}^{(2)} & 0 & 0 & 0 \\ -b_1\hat{y} & M_{22}^{(2)} & -b_3\hat{y} & -M_{24}^{(2)} \\ 0 & e^{-\lambda\tau} & -d_z & -M_{34}^{(2)} \\ -\bar{a}_1^{-1}c_1\hat{u} & -M_{42}^{(2)} & -M_{43}^{(2)} & -M_{44}^{(2)} \end{bmatrix},$$

where

$$M_{11}^{(2)} = a_0 - a_2\hat{y} - a_3\hat{z} - \bar{a}_1^{-1}p_1\hat{u}, \quad M_{22}^{(2)} = b_0 - 2b_2\hat{y} - b_3\hat{z} - \frac{p_2\bar{a}_2\hat{u}}{(\bar{a}_2+\hat{u})^2}$$

$$M_{24}^{(2)} = \frac{p_2\hat{y}}{\bar{a}_2+\hat{y}}, \quad M_{34}^{(2)} = \frac{p_3\hat{z}}{\bar{a}_3+\hat{z}}, \quad M_{44}^{(2)} = -(\xi + \frac{c_2\hat{y}}{\bar{a}_2+\hat{y}} + \frac{c_3\hat{z}}{\bar{a}_3+\hat{z}})$$

$$M_{42}^{(2)} = \frac{\bar{a}_2c_2\hat{u}}{(\bar{a}_2+\hat{y})^2}, \quad M_{43}^{(2)} = \frac{\bar{a}_3c_3\hat{u}}{(\bar{a}_3+\hat{z})^2}.$$

Hence, one of the eigenvalues is

$$\lambda_1^{(2)} = a_0 - a_2\hat{y} - a_3\hat{z} - \bar{a}_1^{-1}p_1\hat{u}.$$

The other eigenvalues satisfy

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0, \tag{2.35}$$

where

$$\begin{aligned} p_2 &= d_z - M_{22}^{(2)} - M_{44}^{(2)} \\ p_1 &= M_{22}^{(2)}M_{44}^{(2)} - d_z(M_{22}^{(2)} + M_{44}^{(2)}) - M_{34}^{(2)}M_{43}^{(2)} - M_{24}^{(2)}M_{42}^{(2)} \\ p_0 &= d_zM_{22}^{(2)}M_{44}^{(2)} - d_zM_{24}^{(2)}M_{42}^{(2)} + M_{34}^{(2)}M_{43}^{(2)}M_{22}^{(2)} \\ q_1 &= b_3\hat{y} \\ q_0 &= -b_3M_{44}^{(2)}\hat{y} - M_{24}^{(2)}M_{42}^{(2)}. \end{aligned}$$

Equation (2.35) is the characteristic polynomial (2.10) in the previous section with new coefficient values. Computing γ, m_2, m_1, m_0 and employing the same arguments as before, we have the following theorems.

Theorem 2.4.2 *Suppose that* $m_2^2 > 3m_1$, $\gamma \leq 0$, $m_2 > 0$ *and* $m_1 > 0$. *Then*

1) if $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the stability of equilibrium* F_2 *is independent of delay* τ *and it remains stable for all* $\tau \geq 0$, *provided that* $a_0 < a_2\hat{y} + a_3\hat{z} + \bar{a}_1^{-1}p_1\hat{u}$,

2) if $p_0 + q_0 \leq 0$, *or* $p_1 + q_1 \leq 0$, *or* $p_2(p_1 + q_1) \leq p_0 + q_0$, *the stability of equilibrium* F_2 *does not depend on* τ *and it remains unstable for all* $\tau \geq 0$.

Theorem 2.4.3 *Assume that either (a)* $m_2 < 0$, $m_1 \geq 0$ *and* $m_2^2 > 3m_1$, *or (b)* $m_1 < 0$ *and* $\gamma < 0$. *Then there exists a positive* $\bar{\tau}$ *such that*

1) if $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the equilibrium* F_2 *remains stable for* $0 \leq \tau \leq \bar{\tau}$ *when* $a_0 < a_2\hat{y} + a_3\hat{z} + \bar{a}_1^{-1}p_1\hat{u}$, *and becomes unstable for all* $\tau \geq \bar{\tau}$,

2) if $p_0 + q_0 \leq 0$, *or* $p_1 + q_1 \leq 0$, *or* $p_2(p_1 + q_1) \leq p_0 + q_0$, *the equilibrium* F_2 *remains unstable for all* $\tau \geq \bar{\tau}$. *As* τ *varies from* 0 *to* $\bar{\tau}$, *at most a finite number of stability switches may occur.*

2.4.3 Global stability

Note that if F_1 is achieved, then healthy cells eventually win the competition with the cancer cells, which is the most desirable result. F_3 represents the coexistence of all four populations. In this section, we derive criteria for the global stabilities of F_1 and F_3 with respect to solutions initiating in $int\,\mathbf{R}_+^4$.

Global stability of F_1

In $int\,\mathbf{R}_+^4$ we choose the Liapunov function,

$$\begin{aligned} V(x(t), y(t), z(t), u(t)) &= x(t) - \bar{x} - \bar{x}\ln(x(t)/\bar{x}) + \alpha_1 y(t) + \frac{1}{2}z^2(t) \\ &+ \frac{1}{2}\alpha_1 b_2 \int_{-\tau}^{0} [y(t+s)]^2 ds + \frac{1}{2}\alpha_2 (u(t) - \bar{u})^2, \end{aligned} \quad (2.36)$$

where α_1, α_2 are positive constants to be determined later. The derivative of (2.36) along solutions of (2.3) is given by

$$\begin{aligned}\dot{V} &= (x-\bar{x})[a_0 - a_1x - a_2y - a_3z - \frac{p_1ux}{\bar{a}_1+x}]\\ &\quad +\alpha_1 y[b_0 - b_1x - b_2y - b_3z - \frac{p_2uy}{\bar{a}_2+y}]\\ &\quad +\frac{1}{2}\alpha_1 b_2[y^2 - (y(t-\tau))^2] + z(cy(t-\tau) - d_zz - \frac{p_3uz}{\bar{a}_3+z})\\ &\quad +\alpha_2(u-\bar{u})[\Delta - (\xi + \frac{c_1x}{\bar{a}_1+x} + \frac{c_2y}{\bar{a}_2+y} + \frac{c_3z}{\bar{a}_3+z})u].\end{aligned}$$

After some computing, we obtain

$$\begin{aligned}\dot{V} &= -(a_1+a_{11})(x-\bar{x})^2 - \alpha_1(\frac{1}{2}b_2+a_{22})y^2 - (d_z+a_{33})z^2\\ &\quad -\frac{1}{2}b_2\alpha_1[(y(t-\tau) - c(b_2\alpha_1)^{-1}z]^2 - \alpha_2(\xi+a_{44})(u-\bar{u})^2\\ &\quad -\{(a_2+b_1\alpha_1)(x-\bar{x})y + (a_{12}+a_{21}\alpha_2)(u-\bar{u})(x-\bar{x}) + b_3\alpha_1yz\\ &\quad +a_3(x-\bar{x})z + a_{14}\alpha_2z(u-\bar{u}) + a_{13}\alpha_2y(u-\bar{u})\}\\ &= -\{\frac{1}{3}(a_1+a_{11})(x-\bar{x})^2 + (a_2+b_1\alpha_1)(x-\bar{x})y + \frac{1}{3}\alpha_1(\frac{1}{2}b_2+a_{22})y^2\}\\ &\quad -\{\frac{1}{3}\alpha_1(\frac{1}{2}b_2+a_{22})y^2 + b_3\alpha_1yz + \frac{1}{3}(d_z+a_{33})z^2\}\\ &\quad -\{\frac{1}{3}(d_z+a_{33})z^2 + a_{14}\alpha_2z(u-\bar{u}) + \frac{1}{3}\alpha_2(\xi+a_{44})(u-\bar{u})^2\}\\ &\quad -\{\frac{1}{3}\alpha_2(\xi+a_{44})(u-\bar{u})^2 + (a_{12}+a_{21}\alpha_2)(u-\bar{u})(x-\bar{x}) + \frac{1}{3}(a_1+a_{11})(x-\bar{x})^2\}\\ &\quad -\{\frac{1}{3}(a_1+a_{11})(x-\bar{x})^2 + a_3(x-\bar{x})z + \frac{1}{3}(d_z+a_{33})z^2\}\\ &\quad -\{\frac{1}{3}\alpha_1(\frac{1}{2}b_2+a_{22})y^2 + a_{13}\alpha_2y(u-\bar{u}) + \frac{1}{3}\alpha_2(\xi+a_{44})(u-\bar{u})^2\}\\ &\quad -\frac{1}{2}b_2\alpha_1[(y(t-\tau) - c(b_2\alpha_1)^{-1}z]^2, \qquad (2.37)\end{aligned}$$

where

$$\begin{aligned}a_{11} &= \frac{\bar{a}_1p_1u}{(\bar{a}_1+\bar{x})(\bar{a}_1+x)}, \quad a_{12} = \frac{p_1\bar{x}}{\bar{a}_1+\bar{x}} \quad a_{13} = \frac{c_2u}{\bar{a}_2+y}, \quad a_{22} = \frac{p_2u}{\bar{a}_2+y}\\ a_{21} &= \frac{\bar{a}_1c_1u}{(\bar{a}_1+\bar{x})(\bar{a}_1+x)}, \quad a_{14} = \frac{c_3u}{\bar{a}_3+z} \quad a_{33} = \frac{p_3u}{(\bar{a}_3+z)} - \frac{c^2}{2\alpha_1b_2}, \quad a_{44} = \frac{c_1\bar{x}}{\bar{a}_2+\bar{x}}.\end{aligned}$$

Note that we have $a_{13}, a_{14}, a_{21} \geq 0$ and

$$\begin{aligned} a_{11} &\leq \frac{p_1\Delta}{\xi(\bar{a}_1 + \bar{x})} =: \bar{a}_{11} \\ a_{22} &\leq p_2\Delta(\bar{a}_2\xi)^{-1} =: \bar{a}_{22} \\ a_{33} + \frac{c^2}{2\alpha_1 b_2} &\leq p_3\Delta(\bar{a}_3\xi)^{-1} =: \bar{a}_{33}. \end{aligned}$$

Therefore, if

$$\begin{aligned} 9b_3^2\alpha_1 &< 4(\frac{1}{2}b_2 + \bar{a}_{22})(d_z + \bar{a}_{33}) \\ 9a_3^2 &< 4(a_1 + \bar{a}_{11})(d_z + \bar{a}_{33}) \\ 9a_{12}^2 &< 4\alpha_2(a_1 + \bar{a}_{11})(\xi + a_{44}) \\ c^2 &< 2\alpha_1 b_2(d_z + p_3\Delta(\bar{a}_3\xi)^{-1}) \\ 9(a_2 + b_1\alpha_1)^2 &< 4\alpha_1(a_1 + \bar{a}_{11})(\frac{1}{2}b_2 + \bar{a}_{22}). \end{aligned} \tag{2.38}$$

Then $\dot{V} < 0$, which leads to the following theorem.

Theorem 2.4.4 *If we choose α_1, α_2 such that (3.28) holds, then F_1 is globally asymptotically stable (see Figure 2.6).*

Global stability of F_3

In $int\, \mathbf{R}_+^4$ we choose the Liapunov function,

$$\begin{aligned} V(x(t), y(t), z(t), u(t)) &= x(t) - x^* - x^* \ln(x(t)/x^*) \\ &\quad + \alpha[y(t) - y^* - y^* \ln(y(t)/y^*)] \\ &\quad + \frac{1}{2}\alpha b_2 \int_{-\tau}^{0} [y(t+s) - y^*]^2 ds \\ &\quad + \frac{1}{2}(z(t) - z^*)^2 \\ &\quad + \frac{1}{2}(u(t) - u^*)^2, \end{aligned} \tag{2.39}$$

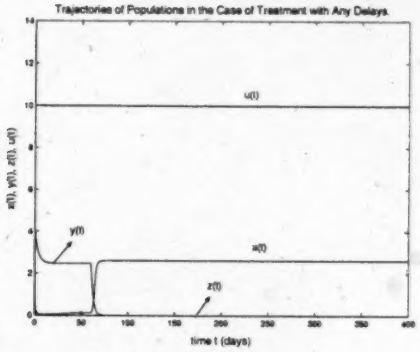

Figure 2.6: A solution for model (2.3) with $a = 3\,day^{-1}, P = 60\,g, f = 0.67, n = 10\,g/kg, k_h = 10\,kg, k_t = 3\,kg, b = 6\,day^{-1}, d_x = d_y = 1\,day^{-1}, m = 20\,g/kg, d_z = 0.2\,day^{-1}, c = 0.3\,day^{-1}, p_1 = 0.0008\,day^{-1}, p_2 = 0.08\,day^{-1}, p_3 = 0.09\,day^{-1}, \bar{a}_1 = 2\,kg, \bar{a}_2 = \bar{a}_3 = 3\,kg, c_1 = 0.0024\,day^{-1}, c_2 = 0.04\,day^{-1}, c_3 = 0.03\,day^{-1}, \Delta = 200\,kg\,day^{-1}, \xi = 20\,day^{-1}$. Here $F_1(2.6015, 0, 0, 9.9887)$ is globally stable, independent of delay. The number of blood vessels drops to zero very fast from the beginning of the treatment. The initial conditions are $x(0) = 1$, $\phi_2(\theta) = 3$, $-\tau \leq \theta \leq 0$, $z(0) = 4$, $u(0) = 14$.

where α is positive constants to be determined later. The derivative of (2.39) along solutions of (2.3) is given by

$$\begin{aligned}
\dot{V} &= (x - x^*)[a_0 - a_1 x - a_2 y - a_3 z - \frac{p_1 u x}{\bar{a}_1 + x}] \\
&\quad + \alpha(y - y^*)[b_0 - b_1 x - b_2 y - b_3 z - \frac{p_2 u y}{\bar{a}_2 + y}] \\
&\quad + \frac{1}{2}\alpha b_2[(y - y^*)^2 - (y(t-\tau) - y^*)^2] \\
&\quad + (z - z^*)(cy(t-\tau) - d_z z - \frac{p_3 u z}{\bar{a}_3 + z}) \\
&\quad + (u - u^*)[\Delta - (\xi + \frac{c_1 x}{\bar{a}_1 + x} + \frac{c_2 y}{\bar{a}_2 + y} + \frac{c_3 z}{\bar{a}_3 + z})u].
\end{aligned}$$

After some computing, we obtain

$$
\begin{aligned}
\dot{V} &= -(a_1+b_{11})(x-x^*)^2-\alpha(\frac{1}{2}b_2+b_{22})(y-y^*)^2-(d_z+b_{33})(z-z^*)^2\\
&\quad -\frac{1}{2}b_2\alpha[(y(t-\tau)-y^*)-c(b_2\alpha)^{-1}(z-z^*)]^2-(\xi+b_{31}+b_{41}+b_{51})(u-u^*)^2\\
&\quad -\{a_3(x-x^*)(z-z^*)+(b_{12}+b_{32})(u-u^*)(x-x^*)+(b_{34}+b_{52})(z-z^*)(u-u^*)\\
&\quad +(a_2+b_1\alpha)(x-x^*)(y-y^*)+b_3\alpha(y-y^*)(z-z^*)+(b_{21}\alpha+b_{42})(y-y^*)(u-u^*)\}\\
&= -\{\frac{1}{3}(a_1+b_{11})(x-x^*)^2+(a_2+b_1\alpha)(x-x^*)(y-y^*)+\frac{1}{3}\alpha(\frac{1}{2}b_2+b_{22})(y-y^*)^2\}\\
&\quad -\{\frac{1}{3}\alpha(\frac{1}{2}b_2+b_{22})(y-y^*)^2+b_3\alpha(y-y^*)(z-z^*)+\frac{1}{3}(d_z+b_{33})(z-z^*)^2\}\\
&\quad -\{\frac{1}{3}(d_z+b_{33})(z-z^*)^2+(b_{34}+b_{52})(z-z^*)(u-u^*)+\frac{1}{3}(\xi+b_{31}+b_{41}+b_{51})(u-u^*)^2\}\\
&\quad -\{\frac{1}{3}(\xi+b_{31}+b_{41}+b_{51})(u-u^*)^2+(b_{12}+b_{32})(u-u^*)(x-x^*)+\frac{1}{3}(a_1+b_{11})(x-x^*)^2\}\\
&\quad -\{\frac{1}{3}(a_1+b_{11})(x-x^*)^2+a_3(x-x^*)(z-z^*)+\frac{1}{3}(d_z+b_{33})(z-z^*)^2\}\\
&\quad -\{\frac{1}{3}\alpha(\frac{1}{2}b_2+b_{22})(y-y^*)^2+(b_{21}\alpha+b_{42})(y-y^*)(u-u^*)\\
&\quad +\frac{1}{3}(\xi+b_{31}+b_{41}+b_{51})(u-u^*)^2\}-\frac{1}{2}b_2\alpha[(y(t-\tau)-y^*)-c(b_2\alpha)^{-1}(z-z^*)]^2, \qquad (2.40)
\end{aligned}
$$

where

$$
\begin{aligned}
b_{11} &= \frac{\bar{a}_1p_1u}{(\bar{a}_1+x^*)(\bar{a}_1+x)},\quad b_{12}=\frac{p_1x^*}{\bar{a}_1+x^*},\quad b_{21}=\frac{p_2y^*}{\bar{a}_2+y^*}\\
b_{22} &= \frac{\bar{a}_2p_2u}{(\bar{a}_2+y^*)(\bar{a}_2+y)},\quad b_{31}=\frac{c_1x^*}{\bar{a}_1+x^*},\quad b_{32}=\frac{\bar{a}_1c_1u}{(\bar{a}_1+x^*)(\bar{a}_1+x)}\\
b_{33} &= \frac{\bar{a}_3p_3u}{(\bar{a}_3+z^*)(\bar{a}_3+z)}-\frac{c^2}{2b_2\alpha},\quad b_{34}=\frac{p_3z^*}{\bar{a}_3+z^*},\quad b_{41}=\frac{c_2y^*}{\bar{a}_2+y^*}\\
b_{42} &= \frac{\bar{a}_2c_2u}{(\bar{a}_2+y^*)(\bar{a}_2+y)},\quad b_{51}=\frac{c_3z^*}{\bar{a}_3+z^*},\quad b_{52}=\frac{\bar{a}_3c_3u}{(\bar{a}_3+z^*)(\bar{a}_3+z)}.
\end{aligned}
$$

Note that we have $b_{32}, b_{42}, b_{52} \geq 0$ and

$$
\begin{aligned}
b_{11} &\leq \frac{p_1\Delta}{\xi(\bar{a}_1+x^*)} =: \bar{b}_{11}\\
b_{22} &\leq \frac{p_2\Delta}{\xi(\bar{a}_2+y^*)} =: \bar{b}_{22}\\
b_{33}+\frac{c^2}{2b_2\alpha} &\leq \frac{p_3\Delta}{\xi(\bar{a}_3+z^*)} =: \bar{b}_{33}
\end{aligned}
$$

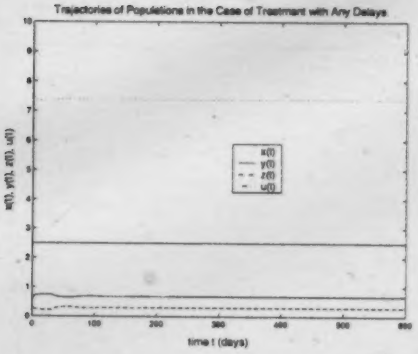

Figure 2.7: A solution for model (2.3) with $a = 3\,day^{-1}, P = 150\,g, f = 0.67, n = 10\,g/kg, k_h = 10\,kg, k_t = 3\,kg, b = 6\,day^{-1}, d_x = d_y = 1\,day^{-1}, m = 20\,g/kg, d_z = 0.2\,day^{-1}, c = 0.09\,day^{-1}, p_1 = 0.0005\,day^{-1}, p_2 = 18\,day^{-1}, p_3 = 2\,day^{-1}, \bar{a}_1 = 20\,kg, \bar{a}_2 = \bar{a}_3 = 800\,kg, c_1 = 0.01\,day^{-1}, c_2 = 36\,day^{-1}, c_3 = 8\,day^{-1}, \Delta = 200\,kg\,day^{-1}, \xi = 80\,day^{-1}$. Here the interior equilibrium $F_3(7.238, 0.9224, 0.5, 2.4986)$ is globally stable, independent of delay. The initial conditions are $x(0) = 7.5, \phi_2(\theta) = 0.5, -\tau \le \theta \le 0, z(0) = 0.3, u(0) = 10$.

Therefore, if

$$\begin{aligned}
9b_3^2\alpha &< 4(\frac{1}{2}b_1 + \bar{b}_{22})(d_z + \bar{b}_{33}) \\
9b_{34}^2 &< 4(d_z + \bar{b}_{33})(\xi + b_{31} + b_{41} + b_{51}) \\
9b_{12}^2 &< 4(\xi + b_{31} + b_{41} + b_{51})(a_1 + \bar{b}_{11}) \\
9a_3^2 &< 4(a_1 + \bar{b}_{11})(d_z + \bar{b}_{33}) \\
9b_{21}^2\alpha &< 4(\frac{1}{2}b_1 + \bar{b}_{22})(\xi + b_{31} + b_{41} + b_{51}) \\
c^2\xi(\bar{a}_3 + z^*) &< 2\alpha b_2 p_3 \Delta \\
9(a_2 + b_1\alpha)^2 &< 4\alpha(a_1 + \bar{b}_{11})(\frac{1}{2}b_1 + \bar{b}_{22}).
\end{aligned} \tag{2.41}$$

Then $\dot{V} < 0$, which leads to the following theorem.

Theorem 2.4.5 *If we choose α such that (2.41), then the interior equilibrium F_3 is globally asymptotically stable (see Figure 2.7).*

2.5 Discussion

From the viewpoint of biological stoichiometry, this chapter dealt with vascular tumor growth and its treatment with chemotherapy techniques. In the absence of treatment, our model is one of the models in Kuang, et al. [60], in which they formulated over a dozen plausible models, then performed extensive simulations on all of them, but they did not give a complete analytical analysis to the models. Therefore, the difference between our work and their work is that they mainly focused on numerical simulations and we mostly focused on analytical analysis. Their extensive simulation work shows that (1) tumor growth and size are very sensitive to the total amount of phosphorus more so than tumor birth rate or death rate is. Phosphorus supply mostly controls and determines a tumor's ultimate size; (2) when several tumor cell species coexist in the tumor, the less malignant type has a high tendency to quickly dominate the tumor and thus push more aggressive tumor cells to metastasize; (3) the time delay τ plays a key role in determining the time for a tumor to reach a given size more dramatically than changes in some other organ values; (4) restricting phosphorus in the body damages both the tumor and the healthy organ. However, selectively limiting phosphorus only to tumor cells will keeping the tumor from reaching a lethal size.

In our analysis in the case of no treatment, we first studied the model equations with regard to invariance of nonnegativity, boundedness of solutions, and the nature of equilibria. Comparing their work to ours, one can find their simulations support very well our theoretical results. The expression of tumor steady state size ($\hat{y}$ and/or y^*) in our analysis shows that the phosphorus value P does play a clear and prominent role in determining its value as confirmed by simulations in [60]. Also, one can find from those expressions for the tumor steady state size that the tumor dies out if one can increase the tumor's death rate (d_y) or lower the tumor's birth rate (b) to certain threshold values. Here we only consider one type of parenchyma cells, our analytical results are not comparable in terms of the case in which several tumor cell species coexist. With respect to the cell maturity time τ, our analysis and simulations show that it not only dramatically determines the time for tumor cells to reach a given size, but plays an important role in the stabilities of the steady states and the stability switches for the delay system.

In our analysis in this case, necessary and sufficient conditions for Hopf bifurcation of the interior equilibrium to occur were obtained by using the time delay as a bifurcation parameter. Analytically, it is difficult to prove in general whether Hopf bifurcation for delay systems is supercritical or subcritical. However, we see from *Figure* 2.3-2.5 that in our models, we get supercritical bifurcation.

Sufficient criteria was also obtained for the uniform persistence of populations and the extinction of cancer cells. With respect to global stabilities, sufficient conditions were obtained for the cancer-free equilibria and interior equilibrium. Thus, we solved the open problem in [60]. It was shown that the system can be permanent but whenever the boundary equilibrium is stable, the interior equilibrium of the system cannot be globally stable for at least small values of the time delay. Further, in this case, persistence cannot occur at least for small values of the time delay. In particular, *Thoerem* 2.3.5 and 2.3.6 give criteria for no stability switching and *Theorem* 2.3.7 for stability switching in the no treatment case. *Theorem* 2.4.2 and 2.4.3 give criteria for no stability switching and stability switching, respectively, in the presence of continuous treatment case.

Finally, based on all these dynamical behaviors of the drug-free system, a continuous treatment with chemotherapy was considered. The rationale behind this is to use the information about the drug-free system to design a drug protocol. When stopping treatment, we would like the patient to be cured or stay in the stable region of the new system. Here, sufficient criteria was obtained for the extinction of cancer cells. Local and global stabilities of the cancer-free equilibrium was studied by utilizing spectral theory and Liapunov functions. It is important to mention that because of the lack of good biological understanding of the drug functioning, it is not clear how the drug acts on the normal and tumor cells. In this chapter, Holling type II function as drug functional response to cells was proposed to simulate the functional response mathematically. We emphasize that to the best of our knowledge, the actual functional response to cancer cells by a chemotherapy agent is not known; but Holling type II is a reasonable starting point based on ecological modeling. Recent work [59] indicated that a ratio-dependent functional response makes more sense and fits the data better than Holling type II. In the future, we will consider this type of functional response as a model of the drug function.

This chapter deals with some aspects of angiogenesis. We note that this topic is also modelled in [46] and [96]. However, these papers only model single species growth and involve partial differential equations. Hence, our results are not comparable.

Since the medical objectives of cancer treatments are to either eliminate the cancer altogether, or confine cancer cells to a tolerable low level, or at least to terminate the growth of cancer, we hope that our results will suggest how to vary the parameters for those cancer interactions governed by system (2.1) so as to make the treatment more effective.

3

A Reaction-Diffusion Model of Leukemia Treatment by Chemotherapy

3.1 Introduction

Leukemia is a cancer of blood cells and can be described as the disorganization of the hematopoietic system in which a malignant clone of blood cells acts to impede the growth of normal hemopoietic tissue. When leukemia develops, the body produces large numbers of abnormal blood cells. In most types of leukemias, the abnormal cells are white blood cells, and they usually look different from normal blood cells, and do not function properly. Leukemia is either acute or chronic. In acute leukemia, the abnormal blood cells are blasts that remain very immature and cannot carry out their normal functions. The number of blasts increases rapidly, and the disease gets worse quickly. Recent works [69-72] show that the origins of acute leukemia can be found in pluripotent stem cells. In the acute leukemia state a pluripotent stem cell in the bone marrow becomes malignant, proliferates and displaces normal cells in the marrow. These abnormal cells then fill the blood and the marrow and produce a malfunction of the body's immune system. In chronic leukemia, some blast cells are present, but in general, these cells are more mature and can carry out some of their normal functions. Also, the number of blasts increases less rapidly than in

acute leukemia. As a result, patients with chronic leukemia get worse gradually. However, without treatment, even the chronic disorders may be fatal [92,93].

In cancer treatment today, four types of treatment are most commonly used in efforts to obtain long-term periods of disease-free remission. These include surgery, radiotherapy, chemotherapy and immunotherapy. Cancer chemotherapy has demonstrated a definite capacity for controlling disseminated metastatic cancer and is therefore widely used [24,37,63,84]. In cancer chemotherapy, anti-neoplastic drugs are designed to selectively destroy or inhibit the proliferative activity of cancer cells while the normal cells are affected to a lesser extent [24,37].

The ultimate role of mathematical modelling in cancer chemotherapy is to provide a more rational basis for experimental design of the anti-cancer drugs and to make qualitative predictions with regard to the dynamic evolution of the disease based on the cytokinetic parameters of the patient and the drug parametric configuration. The fact that it is reasonable to view the interaction between normal cells and cancer cells as competitive is justified in Freedman [30] and Nani and Freedman [75,85]. In [75], a model of cancer treatment by chemotherapy was presented and conditions for the boundedness of solutions were analyzed. The equilibria and their stabilities, and conditions for the existence of small amplitude periodic solutions were also discussed. Persistence and extinction criteria of the normal cells and cancer cells were also derived. It is well known that the distributions of populations in general, being heterogeneous, depend not only on time, but also on the spatial positions in the habitat. For example, leukemia diffuses within the bone marrow and spread from the marrow to other parts of the body, including the lymph nodes, brain, liver, and spleen. So it is natural and more precise to study the corresponding P.D.E. problem as suggested by the authors in [75]. For a detailed explanation of the ecological background of the problem, the reader is referred to [75]. Motivated by the conception of persistence in [12,33,35], we introduce it into this chapter and establish the existence, uniqueness, boundedness and persistence of the solutions for the mixed boundary condition problem by means of a comparison principle and a monotonicity method, (see e.g. ,[80,97]). The main method used in studying the stability of constant solutions is the spectral analysis of the linearized operators.

The idea of modelling cancer interactions with healthy tissue as a competition process was first proposed by Gatenby [41]. However, his paper did not consider treatment. The first paper to incorporate chemotherapy treatment was Nani and Freedman [75]. An extension to modelling cancer at several sites (metastasis) with chemotherapy treatment was carried out in [85].

Since normal cells and cancer cells are competing for nutrient and space, we assume both cancer and normal cells have the same carrying capacity in the model developed in [75] (see [75] for the derivation of the model) and propose a chemotherapy treatment for the new model. Finally we extend it to the diffusion case to model the spread of cancer within a site (such as leukemia in the bone marrow).

The purpose of this chapter is twofold. Mathematically, we compare the dynamics of our model in the case of no diffusion to the diffusion case. Clinically, we hope to derive criteria on the parameters of the model which lead to the control of cancers, and in particular leukemia, which are simulated by our models.

The organization of this this chapter is as follows. In section 3.2 we describe the model. Section 3.3 deals with the no diffusion case, whereas in section 3.4, we analyze the diffusion case. We conclude with a final section which contains numerical examples to illustrate our results and a short discussion.

3.2 The model

We take as our model of leukemia treatment by chemotherapy a system of reaction diffusion equations where $u_1(x,t)$ represents the density of normal cells, $u_2(x,t)$ the density of leukemia cells, and $v(x,t)$ the density of chemotherapy agents in the affected region at time $t \geq 0$. We view $u_1(x,t)$ and $u_2(x,t)$ as competing for nutrients, oxygen, etc. and we think of $v(x,t)$ as a predator capable of destroying both $u_1(x,t)$ and $u_2(x,t)$, but selectively

is more lethal to $u_2(x,t)$. The model then takes the form

$$\begin{aligned}
\frac{\partial u_1}{\partial t} &= D_1\frac{\partial^2 u_1}{\partial x^2} + \alpha_1 u_1\left(1 - \frac{u_1 + r_{12}u_2}{K}\right) - \frac{p_1 u_1 v}{a_1 + u_1} \\
\frac{\partial u_2}{\partial t} &= D_2\frac{\partial^2 u_2}{\partial x^2} + \alpha_2 u_2\left(1 - \frac{r_{21}u_1 + u_2}{K}\right) - \frac{p_2 u_2 v}{a_2 + u_2} \\
\frac{\partial v}{\partial t} &= D_3\frac{\partial^2 v}{\partial x^2} + \Delta - \left[\xi + \frac{c_1 u_1}{a_1 + u_1} + \frac{c_2 u_2}{a_2 + u_2}\right]v,
\end{aligned} \tag{3.1}$$

with initial conditions

$$u_1(x,0) = u_1^0(x), \quad u_2(x,0) = u_2^0(x), \quad v(x,0) = v^0(x).$$

Since this model is used to simulate the interactions between healtby and cancer cells in the bone marrow (which implies it is a one-dimensional measurable space), and since these cells migrate from the bone marrow into the bloodstream, we take as our boundary conditions *Albedo* (or mixed) boundary conditions of the form with x as one-dimensional variables in the interval $0 \le x \le L$:

$$(\frac{\partial u_1}{\partial x} \pm \gamma_1(u_1 - u_1^c))|_{x=0,L} = 0, \ (\frac{\partial u_2}{\partial x} \pm \gamma_2(u_2 - u_2^c))|_{x=0,L} = 0, \ (\frac{\partial v}{\partial x} \pm \gamma_3(v - v^c))|_{x=0,L} = 0,$$

where (u_1^c, u_2^c, v^c) is some reference concentration of the system. $(u_1^0(x), u_2^0(x), v^0(x))$, is a smooth initial function in the interval $0 \le x \le L$.

The constants in system(3.1) may be interpreted as follows:

α_i, $i = 1, 2$, are the specific birth rates of the normal and cancer cells for small densities.

K is the carrying capacity of cells which could be adequately supported by the environment in the absence of the competing population.

r_{21} is a competition coefficient measuring the effects on cancer cells u_2 caused by the presence of normal cells u_1.

r_{12} is a competition coefficient measuring the effects on normal cells u_1 caused by the presence of cancer cells u_2.

p_i, $i = 1, 2$, are the predation coefficients of $v(x,t)$ on $u_i(x,t)$.

a_i, $i = 1, 2$, determine the rates at which $u_i(x,t)$, in the absence of competition and predation, reaches the carrying capacity.

Δ is the infusion rate of the chemotherapy to the bone marrow.

ξ is the washout rate for the chemotherapy agent within this region.

c_i, $i = 1, 2$ are the combination rates of the chemotherapy agent with the cells. Hence they are proportional to p_i, $i = 1, 2$.

All constants are positive. To make this model more realistic, we impose certain inequalities among the parameters. It is well known that leukemia cells grow at a much faster rate than normal cells, at least in the acute case. Further, if no treatment is offered, most of the time leukemia cells out-compete the normal cells independent of initial conditions. Furthermore, the chemotherapy agent must be considerably more effective in killing leukemia than in killing normal cells in order for the treatment to be effective. These lead to the following sets of inequalities:

$$\alpha_2 > \alpha_1, \quad p_2 >> p_1 .$$

In addition, there are other inequalities which we will list in the next section since they depend on homogeneous steady state values.

3.3 The no diffusion case

In the case of no diffusion, the model is just a special case of the main model discussed in Nani and Freedman [75], and consequently all the results of [75] apply here. The model takes the form

$$\begin{aligned} \frac{du_1}{dt} &= \alpha_1 u_1 \left(1 - \frac{u_1 + r_{12}u_2}{K}\right) - \frac{p_1 u_1 v}{a_1 + u_1} \\ \frac{du_2}{dt} &= \alpha_2 u_2 \left(1 - \frac{r_{21}u_1 + u_2}{K}\right) - \frac{p_2 u_2 v}{a_2 + u_2} \\ \frac{dv}{dt} &= \Delta - \left[\xi + \frac{c_1 u_1}{a_1 + u_1} + \frac{c_2 u_2}{a_2 + u_2}\right] v, \end{aligned} \tag{3.2}$$

with initial conditions

$$u_1(0) = u_1^0 > 0,\ u_2(0) = u_2^0 \geq 0,\ v(0) = v^0 > 0.$$

From [75], the following two results hold.

1. All solutions with positive initial values remain positive.

2. System (3.2) is dissipative.

3.3.1 The homogeneous steady states

From [75], the equilibria in terms of our given parameters are:

$$E_0(0,0,\xi^{-1}\Delta), \quad E_1(\hat{u}_1,0,\hat{v}), \quad E_2(0,\tilde{u}_2,\tilde{v}), \quad E_3(u_1^*,u_2^*,v^*).$$

We carry out the analysis of these steady states, even though it may repeat the analysis in [75], since our results will now be given explicitly in terms of the parameters.

Note that the trivial steady state $E_0(0,0,\xi^{-1}\Delta)$ always exists, and $E_1(\hat{u}_1,0,\hat{v})$, $E_2(0,\tilde{u}_2,\tilde{v})$, $E_3(u_1^*,u_2^*,v^*)$ may or may not exist. In particular $E_1(\hat{u}_1,0,\hat{v})$ represents the steady state where leukemia is eliminated, which is the most desirable state. $E_2(0,\tilde{u}_2,\tilde{v})$ represents the case where the leukemia has completely taken over the site. $E_3(u_1^*,u_2^*,v^*)$ means coexistence, which is only desirable for small numbers of leukemia cells.

The equilibrium $E_1(\hat{u}_1,0,\hat{v})$ exists provided that the algebraic system

$$\begin{aligned} \alpha_1(1-\frac{u_1}{K}) - \frac{p_1 v}{a_1+u_1} &= 0\,, \\ \Delta - [\xi + \frac{c_1 u_1}{a_1+u_1}]v &= 0 \end{aligned} \tag{3.3}$$

has a positive solution $(\hat{u}_1,\hat{v})$.

This system has a unique positive solution provided

$$p_1\Delta < \alpha_1 a_1 \xi\,. \tag{3.4}$$

Necessary and sufficient conditions for (3.3) to have two positive solutions are

$$\begin{aligned} \xi a_1 &< K(\xi+c_1) \\ \xi a_1 < \frac{p_1\Delta}{\alpha_1} &< \frac{\alpha_1[a_1\xi - K(\xi+c_1)]^2}{4K(\xi+c_1)}\,. \end{aligned} \tag{3.5}$$

Analogously, $E_2(0,\tilde{u}_2,\tilde{v})$ exists provided that the algebraic system

$$\alpha_2(1-\frac{u_2}{K}) - \frac{p_2 v}{a_2+u_2} = 0$$

$$\Delta - [\xi + \frac{c_2 u_2}{a_2 + u_2}]v = 0 \tag{3.6}$$

has a positive solution $(\tilde{u}_2, \tilde{v})$.

Similar to the analysis of E_1, system (3.6) has a unique positive solution provided

$$p_2\Delta < \alpha_2 a_2 \xi, \tag{3.7}$$

and exactly two positive solutions if

$$\xi a_2 < K(\xi + c_2)$$
$$\xi a_2 < \frac{p_2\Delta}{\alpha_2} < \frac{\alpha_2[a_2\xi - K(\xi + c_2)]^2}{4K(\xi + c_2)}. \tag{3.8}$$

As a result, we have the following theorems.

Theorem 3.3.1 *If (3.4) holds, then $E_1(\hat{u}_1, 0, \hat{v})$ exists uniquely. If (3.5) holds, then there exists two distinct equilibria of type $E_1(\hat{u}_1, 0, \hat{v})$.*

Theorem 3.3.2 *If (3.7) holds, then $E_2(0, \tilde{u}_2, \tilde{v})$ exists uniquely. If (3.8) holds, there exists two distinct equilibria of type $E_2(0, \tilde{u}_2, \tilde{v})$.*

In the next sections, we will analyze both cases when model(3.2) has only one or several solutions of type $E_1(\hat{u}_1, 0, \hat{v})$, $E_2(0, \tilde{u}_2, \tilde{v})$. Here we have their coordinates. In the case of more than one solution of each type, we consider just the first solution with the following coordinates.

$$\hat{u}_1 = \frac{\alpha_1[K(\xi + c_1) - a_1\xi] \pm \{\alpha_1^2[a_1\xi - K(\xi + c_1)]^2 - 4\alpha_1 K(\xi + c_1)(p_1\Delta - \alpha_1 a_1 \xi)\}^{\frac{1}{2}}}{2\alpha_1(\xi + c_1)},$$
$$\hat{v} = \frac{\Delta(\alpha_1 + \hat{u}_1)}{\xi a_1 + (\xi + c_1)\hat{u}_1},$$
$$\tilde{u}_1 = \frac{\alpha_2[K(\xi + c_2) - a_2\xi] \pm \{\alpha_2^2[a_2\xi - K(\xi + c_2)]^2 - 4\alpha_2 K(\xi + c_2)(p_2\Delta - \alpha_2 a_2 \xi)\}^{\frac{1}{2}}}{2\alpha_2(\xi + c_2)},$$
$$\tilde{v} = \frac{\Delta(\alpha_2 + \tilde{u}_2)}{\xi a_2 + (\xi + c_2)\tilde{u}_2}.$$

3.3.2 Local stability

In order to compute the stability of the various equilibria of system (3.2), we let M be the Jacobian matrix about the point (u_1, u_2, v). Then

$$M = \begin{bmatrix} \alpha_1(1 - \frac{2u_1+r_{12}u_2}{K}) - \frac{a_1p_1v}{(a_1+u_1)^2} & -\frac{\alpha_1r_{12}u_1}{K} & -\frac{p_1u_1}{a_1+u_1} \\ -\frac{\alpha_2r_{21}u_2}{K} & \alpha_2(1 - \frac{r_{21}u_1+2u_2}{K}) - \frac{a_2p_2v}{(a_2+u_2)^2} & -\frac{p_2u_2}{a_2+u_2} \\ -\frac{a_1c_1v}{(a_1+u_1)^2} & -\frac{a_2c_2v}{(a_2+u_2)^2} & -[\xi + \frac{c_1u_1}{a_1+u_1} + \frac{c_2u_2}{a_2+u_2}] \end{bmatrix}.$$

Computing M at $E_0(0, 0, \xi^{-1}\Delta)$, we get

$$M_0 = \begin{bmatrix} \alpha_1 - p_1\Delta(a_1\xi)^{-1} & 0 & 0 \\ 0 & \alpha_2 - p_2\Delta(a_2\xi)^{-1} & 0 \\ -c_1\Delta(a_1\xi)^{-1} & -c_2\Delta(a_2\xi)^{-1} & -\xi \end{bmatrix},$$

and the eigenvalues are

$$\lambda_1 = \alpha_1 - p_1\Delta(a_1\xi)^{-1}, \quad \lambda_2 = \alpha_2 - p_2\Delta(a_2\xi)^{-1}, \quad \lambda_3 = -\xi.$$

As a result, we have:

Theorem 3.3.3 *If $p_1\Delta < \alpha_1a_1\xi$ or $p_2\Delta < \alpha_2a_2\xi$, then $E_0(0, 0, \xi^{-1}\Delta)$ is a hyperbolic saddle point. If $p_1\Delta > \alpha_1a_1\xi$ and $p_2\Delta > \alpha_2a_2\xi$, then $E_0(0, 0, \xi^{-1}\Delta)$ is locally asymptotically stable.*

Computing M at $E_1(\hat{u}_1, 0, \hat{v})$, we obtain

$$M_1 = \begin{bmatrix} \alpha_1(1 - \frac{2\hat{u}_1}{K}) - \frac{a_1p_1\hat{v}}{(a_1+\hat{u}_1)^2} & -\frac{\alpha_1r_{12}\hat{u}_1}{K} & -\frac{p_1\hat{u}_1}{a_1+\hat{u}_1} \\ 0 & \alpha_2(1 - \frac{r_{21}\hat{u}_1}{K}) - \frac{p_2\hat{v}}{a_2} & 0 \\ -\frac{a_1c_1\hat{v}}{(a_1+\hat{u}_1)^2} & -\frac{c_2\hat{v}}{a_2} & -(\xi + \frac{c_1\hat{u}_1}{a_1+\hat{u}_1}) \end{bmatrix}.$$

Hence the eigenvalues are

$$\lambda_2 = \alpha_2(1 - K^{-1}r_{21}\hat{u}_1) - a_2^{-1}p_2\hat{v},$$

$$\sigma(A) = \{\lambda_i \,|\lambda^2 - Tr(A)\lambda + \det(A) = 0, i = 1,3\},$$

where

$$A = \begin{bmatrix} \alpha_1(1 - \frac{2\hat{u}_1}{K}) - \frac{a_1 p_1 \hat{v}}{(a_1+\hat{u}_1)^2} & -\frac{p_1\hat{u}_1}{a_1+\hat{u}_1} \\ -\frac{a_1 c_1 \hat{v}}{(a_1+\hat{u}_1)^2} & -(\xi + \frac{c_1\hat{u}_1}{a_1+\hat{u}_1}) \end{bmatrix}.$$

By the Routh-Hurwitz criteria, if $Tr(A) < 0$ and $\det(A) > 0$, then the eigenvalues of A have negative real parts.

Case 1. $\hat{u}_1 > K/2$.

In this case, we have

$$\begin{aligned} Tr(A) &= \alpha_1(1 - \frac{2\hat{u}_1}{K}) - \frac{a_1 p_1 \hat{v}}{(a_1+\hat{u}_1)^2} - (\xi + \frac{c_1\hat{u}_1}{a_1+\hat{u}_1}) < 0, \\ \det(A) &= -[\alpha_1(1 - \frac{2\hat{u}_1}{K}) - \frac{a_1 p_1 \hat{v}}{(a_1+\hat{u}_1)^2}](\xi + \frac{c_1\hat{u}_1}{a_1+\hat{u}_1}) - \frac{a_1 c_1 p_1 \hat{u}_1 \hat{v}}{(a_1+\hat{u}_1)^3} \\ &= -\alpha_1(1 - \frac{2\hat{u}_1}{K})(\xi + \frac{c_1\hat{u}_1}{a_1+\hat{u}_1}) + \frac{p_1 a_1 \Delta\xi}{(a_1+\hat{u}_1)[a_1\xi + (\xi+a_1)\hat{u}_1]} > 0. \end{aligned}$$

Lemma 3.3.1 *If $\hat{u}_1 > K/2$, then the real part of eigenvalues λ_1, λ_3 are negative.*

Note that in this case we have

$$\lambda_2 = \alpha_2(1 - K^{-1} r_{21}\hat{u}_1) - a_2^{-1} p_2 \hat{v} < \alpha_2(1 - \frac{r_{21}}{2}) - a_2^{-1} p_2 \hat{v}.$$

As a result, we have the following theorem.

Theorem 3.3.4 *Suppose that $\hat{u}_1 > K/2$ and $\alpha_2 \neq \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2^{-1} p_2 \hat{v}$. If $r_{21} < 2$, then $E_1(\hat{u}_1, 0, \hat{v})$ is locally asymptotically stable provided $\alpha_2(1 - \frac{r_{21}}{2}) < a_2^{-1} p_2 \hat{v}$, and $E_1(\hat{u}_1, 0, \hat{v})$ becomes unstable provided $\alpha_2 > \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2^{-1} p_2 \hat{v}$. However, If $r_{21} > 2$, then $E_1(\hat{u}_1, 0, \hat{v})$ locally asymptotically stable.*

Biological implications from Theorem 3.3.4:

(1) The survival of the normal cells depends on the steady state size ($\hat{u}_1$) and the competitive capacity with the cancer cells (r_{21}). *Theorem* 3.4.4 shows that if the steady

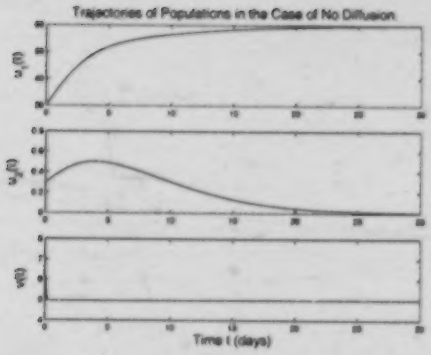

Figure 3.1: Solutions for model (3.2) with $\alpha_1 = 0.5\,day^{-1}, \alpha_2 = 1.0\,day^{-1}, K = 60.0\,mg, r_{12} = 8, r_{21} = 1, p_1 = 0.0008\,day^{-1}, p_2 = 0.05\,day^{-1}, a_1 = 1.0\,mg, a_2 = 1.0\,mg, c_1 = 0.008\,day^{-1}, c_2 = 0.5,\ day^{-1}, \Delta = 100.0\,mg\,day^{-1}, \xi = 20\,day^{-1}; u_1(0) = 30.0\,mg, u_2(0) = 0.3\,mg, v(0) = 8.0\,mg$. Here the boundary equilibrium $E_1(60.0, 0, 5.0)$ is locally stable. The cancer cells initially grow but eventually decrease and are driven to extinction. This is due to the heavy dose of chemotherapy drugs, which inhibits the proliferative capacities of the cancer cells and causes damage to the cancer growth.

state size of the normal cells is greater than the half size of the carrying capacity ($\hat{u}_1 > K/2$), then normal cells may survive the treatment and the body remains healthy. Also, if the normal cells are more competitive ($r_{21} > 2$), thus inhibiting the proliferative capacities of cancer cells, then the normal cells may eventually win the competition (see *Figure* 3.1), i.e. if the stability is global.

(2) The survival of the cancer cells depends on the growth rate (α_2), the competitive ability of the normal cells (r_{21}), and the intensity of the treatment ($a_2^{-1}p_2$) applied to the cancer cells. If the intensity of the treatment to the cancer cells is relatively weak (small value of $a_2^{-1}p_2$) and cancer grows very rapidly (large value of α_2) and the normal cells are less competitive ($r_{21} < 2$) such that $\alpha_2 > \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2^{-1}p_2\hat{v}$, then the cancer cells will survive the treatment and win the competition with the normal cells. Thus, cancer will accumulate and begin to grow.

Case 2. $\hat{u}_1 < K/2$.

In this case we obtain

$$\lambda_2 = \alpha_2(1 - K^{-1}r_{21}\hat{u}_1) - a_2^{-1}p_2\hat{v} > \alpha_2(1 - \frac{r_{21}}{2}) - a_2^{-1}p_2\hat{v}.$$

Theorem 3.3.5 *Suppose that $\hat{u}_1 < K/2$ and $\alpha_2 \neq \alpha_2 K^{-1}\hat{u}_1 + a_2^{-1}p_2\hat{v}$. Then $E_1(\hat{u}_1, 0, \hat{v})$ becomes unstable if $\alpha_2 > \alpha_2 r_{21}/2 + a_2^{-1}p_2\hat{v}$ and the cancer population begins to grow.*

*Theorem*3.3.5 shows that in the absence of any treatment ($p_2 = 0$) a necessary condition for cancer growth is that the competition effect of the normal cells on the cancer cells is less than a certain value (since $\alpha_2 > \alpha_2 r_{21}/2 + a_2^{-1}p_2\hat{v}$ implies that $r_{21} < 2$), which is consistent with the development of cancer cells in patients. When applying treatment, the cancer cells will also survive the treatment if the growth rate α_2 is sufficiently large and the intensity of treatment is relatively weak (small value of $a_2^{-1}p_2$).

Computing M at $E_2(0, \tilde{u}_2, \tilde{v})$, one obtains

$$M_2 = \begin{bmatrix} \alpha_1(1 - \frac{r_{12}\tilde{u}_2}{K}) - \frac{p_1\tilde{v}}{a_1} & 0 & 0 \\ -\frac{\alpha_2 r_{21}\tilde{u}_2}{K} & \alpha_2(1 - \frac{2\tilde{u}_2}{K}) - \frac{a_2 p_1\tilde{v}}{(a_2+\tilde{u}_2)^2} & -\frac{p_2\tilde{u}_2}{a_2+\tilde{u}_2} \\ -\frac{c_1\tilde{v}}{a_1} & -\frac{a_2 c_2\tilde{v}}{(a_2+\tilde{u}_2)^2} & -[\xi + \frac{c_2\tilde{u}_2}{a_2+\tilde{u}_2}] \end{bmatrix}.$$

Hence the eigenvalues are

$$\lambda_1 = \alpha_1(1 - K^{-1}r_{12}\tilde{u}_2) - a_1^{-1}p_1\tilde{v},$$

$$\sigma(B) = \{\lambda_i \,|\lambda^2 - Tr(B)\lambda + \det(B) = 0, i = 2, 3\},$$

where

$$B = \begin{bmatrix} \alpha_2(1 - \frac{2\tilde{u}_2}{K}) - \frac{a_2 p_2\tilde{v}}{(a_2+\tilde{u}_2)^2} & -\frac{p_2\tilde{u}_2}{a_2+\tilde{u}_2} \\ -\frac{a_1 c_1\tilde{v}}{(a_2+\tilde{u}_2)^2} & -[\xi + \frac{c_2\tilde{u}_2}{a_2+\tilde{u}_2}] \end{bmatrix}.$$

Similar to the analysis of E_1, we have the following Lemma.

Lemma 3.3.2 *If $\tilde{u}_2 > K/2$, then the real parts of eigenvalues λ_2, λ_3 are negative.*

Based on *Lemma* 3.3.2, we have the following theorem.

Theorem 3.3.6 *Suppose that $\tilde{u}_2 > K/2$ and $\alpha_1 \neq \alpha_1 K^{-1} r_{12}\tilde{u}_2 + a_1^{-1}p_1\tilde{v}$. If $r_{12} < 2$, then $E_2(0, \tilde{u}_2, \tilde{v})$ is locally asymptotically stable provided $\alpha_1(1 - \frac{r_{12}}{2}) < a_1^{-1}p_1\tilde{v}$, and $E_2(0, \tilde{u}_2, \tilde{v})$ becomes unstable provided $\alpha_1 > \alpha_1 K^{-1} r_{12}\tilde{u}_2 + a_1^{-1}p_1\tilde{v}$. However, if $r_{12} > 2$, then $E_2(0, \tilde{u}_2, \tilde{v})$ locally asymptotically stable.*

Biological implications from Theorem 3.3.6:

(1) The survival of the cancer cells is dependent on the steady state size ($\tilde{u}_2$) and the competitive capacity with the normal cells (r_{12}). *Theorem*3.3.6 demonstrates that if the steady state size of cancer cells is greater than the half size of the carrying capacity ($\tilde{u}_2 > K/2$) and the cancer cells are more competitive and inhibit the growth of the normal cells ($r_{12} > 2$), then the cancer cells will dominate the normal cells and survive the treatment (see *Figure* 3.2).

(2) The survival of the normal cells depends on the growth rate (α_1), the competitive capacity of cancer cells (r_{12}) and the intensity treatment ($a_1^{-1}p_1$) applied to the normal cells. *Theorem* 3.3.6 shows that if the drug is selectively less lethal to the normal cells (small value of $a_1^{-1}p_1$) and they grow rapidly (large value of α_1) and the cancer cells are less competitive (small value of r_{12}) such that $\alpha_1 > \alpha_1 K^{-1} r_{12}\tilde{u}_2 + a_1^{-1}p_1\tilde{v}$, then the normal cells will recover their growth and win the competition with the cancer cells (small value of $a_1^{-1}p_1$).

Theorem 3.3.7 *Suppose that $\tilde{u}_2 < K/2$ and $\alpha_1 \neq \alpha_1 K^{-1} r_{12}\tilde{u}_2 + a_2^{-1}p_1\tilde{v}$. Then $E_2(0, \tilde{u}_2, \tilde{v})$ becomes unstable if $\alpha_1 > \alpha_1 r_{21}/2 + a_1^{-1}p_1\tilde{v}$ and the normal cells recover their growth.*

Theorem 3.3.7 shows that in the absence of any treatment ($p_1 = 0$) a necessary condition for the normal cells to grow is that the competition effect of the cancer cells on normal cells is less than a certain value (since $\alpha_1 > \alpha_1 r_{21}/2 + a_1^{-1}p_1\tilde{v}$ implies that $r_{12} < 2$).

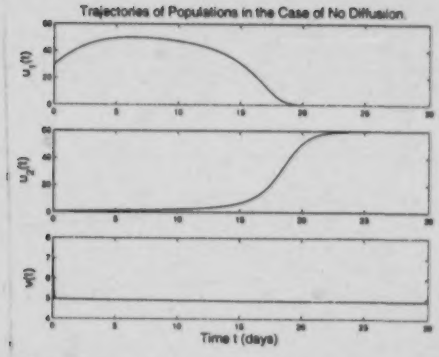

Figure 3.2: Solutions for model (3.2) approach $E_2(0, 60.0, 5.0)$ if the treatment intensity is weak (small values of ${a_2}^{-1}p_2$ and/or $\xi^{-1}\Delta$). Here other parameters and initial conditions are the same as in *Figure* 3.1 except $p_2 = 0.01$. *Figure* 3.2 shows that (1) the normal cells grow at the beginning due to their large initial size but eventually lose the competition with the cancer cells and decrease to zero due to the weak intensity treatment(small p_2), and (2) the cancer cells accumulate persistently at the beginning and take about 20 days to dominate the normal cells. This is due to the weak intensity of the treatment.

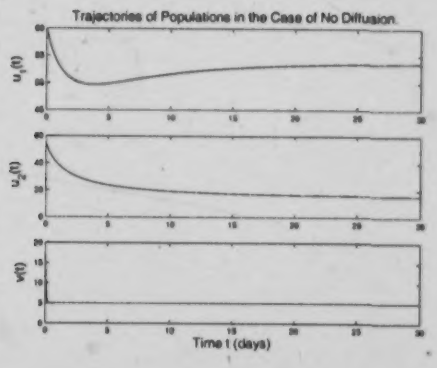

Figure 3.3: A solution for model (3.2) with $\alpha_1 = 0.5\,day^{-1}, \alpha_2 = 0.8\,day^{-1}, K = 60\,mg, r_{12} = 0.4, r_{21} = 0.3, p_1 = 0.0008\,day^{-1}, p_2 = 8.0\,day^{-1}, a_1 = 80.0\,mg, a_2 = 90.0\,mg, c_1 = 0.008\,day^{-1}, c_2 = 0.5\,day^{-1}, \Delta = 100.0\,mg\,day^{-1}, \xi = 20.0\,day^{-1}; u_1(0) = 60.0\,mg, u_2(0) = 58.0\,mg, v(0) = 20.0\,mg$. Here system (2) is uniformly persistent and the interior equilibrium $E_3(53.0, 18.1, 5.0)$ is locally stable. Here also the drug is selectively lethal to the cancer cells and controls it at a lower level than the normal cells

When applying treatment, normal cells will also survive the treatment if its growth rate α_1 is sufficiently large and the drug is less lethal to normal cells.

Now we wish to examine criteria for there to be no limit cycles in the $u_1 - v$ plane, $u_2 - v$ plane, and the $u_1 - u_2$ plane.

In the $u_1 - v$ plane:

$$\begin{aligned} \frac{du_1}{dt} &= \alpha_1 u_1(1 - \frac{u_1}{K}) - \frac{p_1 u_1 v}{a_1 + u_1} \\ \frac{dv}{dt} &= \Delta - [\xi + \frac{c_1 u_1}{a_1 + u_1}]v. \end{aligned}$$

Using Dulac's negative criterion, we define

$$\begin{aligned} D(u_1, v) &= \frac{\partial}{\partial u_1}[\frac{a_1 + u_1}{p_1 u_1}(\alpha_1 u_1(1 - \frac{u_1}{K}) - \frac{p_1 u_1}{a_1 + u_1}v)] + \frac{\partial}{\partial v}[\frac{a_1 + u_1}{p_1 u_1}(\Delta - (\xi + \frac{c_1 u_1}{a_1 + u_1}))v] \\ &= \frac{\alpha_1(K - a_1)}{p_1 K} - \frac{2\alpha_1 u_1}{p_1 K} - \frac{\xi(a_1 + u_1)}{p_1 u_1} - \frac{c_1}{p_1}. \end{aligned}$$

Clearly, $D(u_1, v) < 0$ for $u_1, v > 0$ if $K < a_1$. Therefore, if $K < a_1$, then there are no periodic solutions in the $u_1 - v$ plane.

A similar statement holds for the corresponding system in the $u_2 - v$ plane, that is, if $K < a_2$, then there are no periodic solutions in the $u_2 - v$ plane.

Since there is no equilibrium in the $u_1 - u_2$ plane, there are no periodic solutions in this plane.

Based on the above results, we may address the question of an interior equilibrium in $u_1 - u_2 - v$ space by using the techniques in Freedman and Waltman [12,35], and the results in Butler et al. [12], and obtain the following theorem.

Theorem 3.3.8 *Suppose that* $K \leq \min\{a_1, a_2, 2\hat{u}_1, 2\tilde{u}_2\}$. *If* $\alpha_1 > \alpha_1 K^{-1} r_{12}\tilde{u}_2 + a_1^{-1} p_1 \tilde{v}$ *and* $\alpha_2 > \alpha_2 K^{-1} r_{21}\hat{u}_2 + a_2^{-1} p_2 \hat{v}$, *then system (3.2) is uniformly persistent, and hence* $E_3(u_1^*, u_2^*, v^*)$ *exists.*

Theorem 3.3.8 shows that there exists a situation in which all populations will eventually survive the treatment and globally coexist in the long-term run if the environmental carrying capacity is small enough (see *Figure* 3.3).

3.4 The diffusion case.

To study the effects of spatial variations, we first note that the non-uniform diffusive steady state produces equations that can not be solved in closed form. We therefore consider the effects of small space - time perturbations of the uniform steady states, E_0, E_1, E_2, E_3. Before we study the stabilities of these steady states, we first establish the existence and uniqueness of solutions of system (3.1).

3.4.1 Preliminaries

In this section we introduce the concept of upper and lower solutions as well as an existence-comparison theorem, which will be very useful to us in establishing the existence, uniqueness, and boundedness, and even in studying the asymptotic behavior (in some sense) of the solutions.

We first consider the more general system

$$\begin{aligned}
\frac{\partial u_1}{\partial t} - \nabla^2 u_1 &= f_1(u_1, u_2, u_3), \\
\frac{\partial u_2}{\partial t} - \nabla^2 u_2 &= f_2(u_1, u_2, u_3), \\
\frac{\partial u_3}{\partial t} - \nabla^2 u_3 &= f_3(u_1, u_2, u_3),
\end{aligned} \tag{3.9}$$

with boundary condition

$$B_i[u_i] = \alpha_i(x)u_i + \beta_i(x)\tfrac{\partial u_i}{\partial n} = h_i(x), \quad i = 1,2,3 \text{ on } \partial\Omega \times \Re^+,$$

and initial condition

$u_i(x,0) = u_i^0(x)$, $i = 1,2,3$ in an open boundary region Ω with smooth boundary $\partial\Omega$.

We assume that α_i, β_i, h_i and u_i^0 are smooth nonnegative functions with $u_i^0 \neq 0$, $\alpha_i + \beta_i > 0$ and that f_i is continuously differentiable with respect to its variables for $u_k \geq 0$, $i,k = 1,2,3$. In addition, we require that $f = (f_1, f_2, f_3)$ is a quasi-monotone

function, i.e.:

$$\frac{\partial f_i}{\partial u_j} \leq 0,\ i = 1,2,3,\ j = 1,2,3,\ i \neq j,$$

for $u_i \geq 0,\ i = 1,2,3.$

Now, we give the definition of upper and lower solutions.

Definition 3.1 Ordered smooth functions $\bar{u} = (\bar{u}_1, \bar{u}_2, \bar{u}_3)$ and $\underline{u} = (\underline{u}_1, \underline{u}_2, \underline{u}_3)$ in Ω_T are called upper and lower solutions of (3.9) respectively, if they satisfy the following inequalities

$$(\bar{u}_1)_t - \nabla^2 \bar{u}_1 - f_1(\bar{u}_1, \underline{u}_2, \underline{u}_3) \geq (\underline{u}_1)_t - \nabla^2 \underline{u}_1 - f_1(\underline{u}_1, \bar{u}_2, \bar{u}_3)$$

$$(\bar{u}_2)_t - \nabla^2 \bar{u}_2 - f_2(\underline{u}_1, \bar{u}_2, \underline{u}_3) \geq (\underline{u}_2)_t - \nabla^2 \underline{u}_2 - f_2(\bar{u}_1, \underline{u}_2, \bar{u}_3)$$

$$(\bar{u}_3)_t - \nabla^2 \bar{u}_3 - f_3(\underline{u}_1, \underline{u}_2, \bar{u}_3) \geq (\underline{u}_3)_t - \nabla^2 \underline{u}_3 - f_3(\bar{u}_1, \bar{u}_2, \underline{u}_3)$$

in Ω_T ,where $\Omega_T = \Omega \times (0,T]$.

$B_i[\bar{u}_i] \geq h_i(x) \geq B_i[\underline{u}_i],\ i = 1,2,3,$ on S_T; $\bar{u}_i(x,0) \geq u_i^0(x) \geq \underline{u}_i(x,0),\ i = 1,2,3,$ on Ω, where $S_T = \partial\Omega \times (0,T]$, and $T < \infty$ but can be arbitrarily large.

Suppose $\bar{u}$ and $\underline{u}$ exist. Denote

$$\Sigma = \{(u_1,u_2,u_3) \in \Re^3 : \underline{\rho}_i \leq u_i \leq \bar{\rho}_i, i = 1,2,3\}$$

$$M_i = \sup_{\Sigma}\{\frac{\partial f_i}{\partial u_i}\}, \quad i = 1,2,3,$$

where $\underline{\rho}_i = \inf_{(x,t)\in\Omega_T} \underline{u}_i(x,t)$, $\bar{\rho}_i = \sup_{(x,t)\in\Omega_T} \bar{u}_i(x,t)$, $i = 1,2,3.$

We construct the sequences $\{\bar{u}^{(k)}\}$ and $\{\underline{u}^{(k)}\}$ with $\bar{u}^{(0)} = \bar{u}$ and $\underline{u}^{(0)} = \underline{u}$ as follows:

$$(\bar{u}_1^{(k)})_t - \nabla^2 \bar{u}_1^{(k)} + M_1 \bar{u}_1^{(k)} = M_1 \bar{u}_1^{(k-1)} + f_1(\bar{u}_1^{(k-1)}, \underline{u}_2^{(k-1)}, \underline{u}_3^{(k-1)})$$

$$(\bar{u}_2^{(k)})_t - \nabla^2 \bar{u}_2^{(k)} + M_2 \bar{u}_2^{(k)} = M_2 \bar{u}_2^{(k-1)} + f_2(\underline{u}_1^{(k-1)}, \bar{u}_2^{(k-1)}, \underline{u}_3^{(k-1)})$$

$$(\bar{u}_3^{(k)})_t - \nabla^2 \bar{u}_3^{(k)} + M_3 \bar{u}_3^{(k)} = M_3 \bar{u}_3^{(k-1)} + f_3(\underline{u}_1^{(k-1)}, \underline{u}_2^{(k-1)}, \bar{u}_3^{(k-1)})$$

$$(\underline{u}_1^{(k)})_t - \nabla^2 \underline{u}_1^{(k)} + M_1 \underline{u}_1^{(k)} = M_1 \underline{u}_1^{(k-1)} + f_1(\underline{u}_1^{(k-1)}, \bar{u}_2^{(k-1)}, \bar{u}_3^{(k-1)})$$

$$(\underline{u}_2^{(k)})_t - \nabla^2 \underline{u}_2^{(k)} + M_2 \underline{u}_2^{(k)} = M_2 \underline{u}_2^{(k-1)} + f_2(\bar{u}_1^{(k-1)}, \underline{u}_2^{(k-1)}, \bar{u}_3^{(k-1)})$$
$$(\underline{u}_3^{(k)})_t - \nabla^2 \underline{u}_3^{(k)} + M_3 \underline{u}_3^{(k)} = M_3 \underline{u}_3^{(k-1)} + f_3(\bar{u}_1^{(k-1)}, \bar{u}_2^{(k-1)}, \underline{u}_3^{(k-1)}),$$

and

$$B_i[\bar{u}_i^{(k)}] = h_i(x) = B_i[\underline{u}_i^{(k)}], \quad i = 1,2,3, (x,t) \in S_T,$$
$$\bar{u}_i^{(k)}(x,0) = u_i^0(x) = \underline{u}_i^{(k)}(x,0), \quad i = 1,2,3, \quad x \in \Omega.$$

By using standard techniques (e.g. C. V. Pao [80]), we can establish the following existence - comparison theorem.

Theorem 3.4.1 *For system (3.9), suppose that $f = (f_1, f_2, f_3)$ is a quasi-monotone function and there exists a pair of upper and lower solutions $\bar{u} = (\bar{u}_1, \bar{u}_2, \bar{u}_3)$ and $\underline{u} = (\underline{u}_1, \underline{u}_2, \underline{u}_3)$ satisfying $\underline{u}_i \leq \bar{u}_i$, $i = 1,2,3$. Then the sequences $\{\bar{u}^{(k)}\}$ and $\{\underline{u}^{(k)}\}$ obtained as above converge monotonically from above and below, respectively, to a unique solution $u = (u_1, u_2, u_3)$ of (3.9) such that*

$$\underline{u}_i(x,t) \leq u_i(x,t) \leq \bar{u}_i(x,t), i = 1,2,3, (x,t) \in \Omega_T.$$

In view of *Theorem* 3.4.1, to obtain the existence and uniqueness of solutions of (3.1), we need only to find a pair of upper and lower solutions of (3.1). We do this as follows by using an appropriate O.D.E. problem to find upper and lower solutions.

For an upper solution, we study the O.D.E. system

$$\begin{aligned} \frac{du_1}{dt} &= \alpha_1 u_1 (1 - \frac{u_1}{K}) \\ \frac{du_2}{dt} &= \alpha_2 u_2 (1 - \frac{u_2}{K}) \\ \frac{dv}{dt} &= \Delta - \xi v, \end{aligned}$$

with initial conditions

$$u_i(0) = \tilde{u}_i \equiv \sup_{\Omega} u_i^0(x) > 0, i = 1,2,3, \; v(0) = \tilde{v} \equiv \sup_{\Omega} v^0(x) > 0.$$

Then we have

$$\bar{u}_1(t) = K[1 + \frac{K - \tilde{u}_1}{\tilde{u}_1} e^{-\alpha_1 t}]^{-1},$$

$$\bar{u}_2(t) = K[1 + \frac{K - \tilde{u}_2}{\tilde{u}_2} e^{-\alpha_2 t}]^{-1},$$
$$\bar{v}(t) = \Delta\xi^{-1} + (\tilde{v} - \Delta\xi^{-1})e^{-t\xi}.$$

Clearly, $(0,0,0)$ and $(\bar{u}_1(t), \bar{u}_2(t), \bar{v}(t))$ are a pair of lower and upper solutions of (3.1). Hence we can use *Theorem* 3.4.1 for any $T > 0$ and obtain:

Theorem 3.4.2 *There exists a unique solution* $(u_1(x,t), u_2(x,t), v(x,t))$ *to system (3.1) satisfying*

$$0 \le u_i(x,t) \le \bar{u}_i(t), \quad i = 1,2, \quad 0 \le v(x,t) \le \bar{v}(t).$$

We have established the global existence and uniqueness of the solutions of (3.1). Now, we will prove the global boundedness of these solutions.

From the above, it is easy to see that

$$0 \le u_1(x,t) \le \bar{u}_1(t) \le \max\{K, \tilde{u}_1\},$$
$$0 \le u_2(x,t) \le \bar{u}_2(t) \le \max\{K, \tilde{u}_2\},$$
$$0 \le v(x,t) \le \bar{v}(t) \le \max\{\Delta\xi^{-1}, \tilde{v}\}.$$

Hence, all solutions of (3.1) are uniformly bounded for $(x,t) \in \Omega \times R^+$.

Next, we analyze the asymptotic behavior of the three populations.

Theorem 3.4.3 *Suppose that* $\alpha_1 - \alpha_1 r_{12} - a_1^{-1}\xi^{-1}p_1\Delta > 0$, $\alpha_2 - \alpha_2 r_{21} - a_2^{-1}\xi^{-1}p_2\Delta > 0$. *Then system (3.1) is persistent.*

Proof. We are trying to find a pair of upper and lower solutions with the property:

$$\begin{aligned}
\frac{d\bar{u}_1(t)}{dt} &= \alpha_1\bar{u}_1(1 - \frac{\bar{u}_1 + r_{12}\underline{u}_2}{K}) \\
\frac{d\bar{u}_2(t)}{dt} &= \alpha_2\bar{u}_2(1 - \frac{r_{21}\underline{u}_1 + \bar{u}_2}{K}) \\
\frac{d\bar{v}(t)}{dt} &= \Delta - \bar{v}\xi,
\end{aligned}$$

and

$$\begin{aligned}
\frac{d\underline{u}_1(t)}{dt} &= \alpha_1\underline{u}_1(1-\frac{\underline{u}_1+r_{12}K}{K})-a_1^{-1}p_1\underline{u}_1\bar{v}\\
\frac{d\underline{u}_2(t)}{dt} &= \alpha_2\underline{u}_2(1-\frac{r_{21}K+\underline{u}_2}{K})-a_2^{-1}p_2\underline{u}_2\bar{v}\\
\frac{d\underline{v}(t)}{dt} &= \Delta-[\xi+a_1^{-1}c_1K+a_2^{-1}c_2K]\underline{v},
\end{aligned}$$

with initial conditions

$$\bar{u}_i(0)=\tilde{u}_i\equiv\sup_\Omega u_i^0(x)>0,\quad \bar{v}(0)=\tilde{v}^0\equiv\sup_\Omega v^0(x)>0,\quad i=1,2,$$

and

$$\underline{u}_i(0)=\underline{\tilde{u}}_i\equiv\inf_\Omega u_i^0(x)>0,\quad \underline{v}(0)=\underline{\tilde{v}}^0\equiv\inf_\Omega v^0(x)>0,\quad i=1,2.$$

Here, we take $K=\max\{K,\tilde{u}_i\}$, $i=1,2$ for convenience.

Obviously, $(\tilde{u}_1,\tilde{u}_2,\bar{v})$ and $(\underline{u}_1,\underline{u}_2,\underline{v})$ are a pair of lower and upper solutions of (3.1); moreover, we have

$$\bar{v}(t)=\Delta\xi^{-1}+(\tilde{v}^0-\Delta\xi^{-1})e^{-t\xi},$$

$$\begin{aligned}
\underline{v}(t) &= \Delta(\xi+a_1^{-1}c_1K+a_2^{-1}c_2K)^{-1}\\
&\quad+[\tilde{v}^0-\Delta(\xi+a_1^{-1}c_1Ka_2^{-1}c_2K)^{-1}]e^{-t(\xi+a_1^{-1}c_1K+a_2^{-1}c_2K)}.
\end{aligned}$$

Therefore,

$$\liminf_{t\to\infty}\underline{v}(t)=\Delta(\xi+a_1^{-1}c_1K+a_2^{-1}c_2K)^{-1}>0,$$

$$\liminf_{t\to\infty}v(x,t)\geq\liminf_{t\to\infty}\underline{v}(t)=\Delta(\xi+a_1^{-1}c_1K+a_2^{-1}c_2K)^{-1}>0.$$

Again,

$$\underline{u}_1(t)=\frac{(\alpha_1-\alpha_1r_{12}-a_1^{-1}p_1\bar{v})ce^{(\alpha_1-\alpha_1r_{12}-a_1^{-1}p_1\bar{v})t}}{1+\alpha_1K^{-1}ce^{(\alpha_1-\alpha_1r_{12}-a_1^{-1}p_1\bar{v})t}},$$

where c is a constant. Hence

$$\liminf_{t\to\infty}u_1(x,t)\geq\liminf_{t\to\infty}\underline{u}_1(x,t)=\frac{\alpha_1-\alpha_1r_{12}-a_1^{-1}\xi^{-1}p_1\Delta}{\alpha_1K^{-1}}>0.$$

Similarly, we have

$$\liminf_{t\to\infty} u_2(x,t) \geq \liminf_{t\to\infty} \underline{u}_2(x,t) = \frac{\alpha_2 - \alpha_2 r_{21} - a_2^{-1}\xi^{-1}p_2\Delta}{\alpha_2 K^{-1}} > 0.$$

The proof is complete. □

Generally, normal and abnormal cells are competing for resources, such as oxygen, nutrients and space. Cancer cells not only compete with those healthy cells for resources, but also compete with each other and against healthy cells throughout the body for the same resources. Therefore, normal cells and cancer cells have different competition effects on each other (different values of r_{12} and r_{21}). *Theorem* 3.4.3 demonstrates that the treatment and the competition capacities of both populations play an important role in the persistence of the system, and if one of populations eventually wins the competition, then the system (3.1) cannot persist.

Now we will analyze the stability of all possible equilibria for system (3.1),

$$E_0(0,0,\xi^{-1}\Delta), \quad E_1(\hat{u}_1,0,\hat{v}), \quad E_2(0,\tilde{u}_2,\tilde{v}), \quad E_3(u_1^*,u_2^*,v^*).$$

By linearizing (3.1) around a uniform steady state $E(u_1^c,u_2^c,v^c)$, we obtain

$$\begin{aligned}
\frac{\partial u_1}{\partial t} &= D_1\frac{\partial^2 u_1}{\partial x^2} + a_{11}(u_1-u_1^c) + a_{12}(u_2-u_2^c) + a_{13}(v-v^c)\\
\frac{\partial u_2}{\partial t} &= D_2\frac{\partial^2 u_2}{\partial x^2} + a_{21}(u_1-u_1^c) + a_{22}(u_2-u_2^c) + a_{23}(v-v^c)\\
\frac{\partial v}{\partial t} &= D_3\frac{\partial^2 v}{\partial x^2} + a_{31}(u_1-u_1^c) + a_{32}(u_2-u_2^c) + a_{33}(v-v^c).
\end{aligned}$$

Here the one-dimensional boundary conditions in the interval $0 \leq x \leq L$ are:

$$(\frac{\partial u_1}{\partial x} \pm \gamma_1(u_1-u_1^c))|_{x=0,L} = 0, \ (\frac{\partial u_2}{\partial x} \pm \gamma_2(u_2-u_2^c))|_{x=0,L} = 0, \ (\frac{\partial v}{\partial x} \pm \gamma_3(v-v^c))|_{x=0,L} = 0.$$

The above Albedo BCs can be maintained in time by controlling the diffusive flow of u_1, u_2 and v through the boundaries. For those BCs, (u_1^c,u_2^c,v^c) remain as the homogeneous steady state for $0 < \gamma_i \leq \infty$, $i = 1,2,3$.

We are looking for stability in the homogeneous steady state by using the linear stability theory. As usual, we propose for u_1, u_2 and v the perturbed forms:

$$\begin{aligned} u_1(x,t) &= u_1^c + \varepsilon_1(x,t) \\ u_2(x,t) &= u_2^c + \varepsilon_2(x,t) \\ v(x,t) &= v^c + \varepsilon_3(x,t). \end{aligned}$$

This leads to the following linear system for the small space and time-dependent perturbations:

$$\frac{\partial}{\partial t}\begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{bmatrix} = \begin{bmatrix} a_{11} + D_1\frac{\partial^2}{\partial x^2} & a_{12} & a_{13} \\ a_{21} & a_{22} + D_2\frac{\partial^2}{\partial x^2} & a_{23} \\ a_{31} & a_{32} & a_{33} + D_1\frac{\partial^2}{\partial x^2} \end{bmatrix}\begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{bmatrix} \tag{3.10}$$

By linearity, the BCs to be fulfilled by the perturbations at the boundaries are:

$$\frac{\partial \varepsilon_i}{\partial x}\mid_{x=0,L} = \mp\gamma_i\epsilon_i \mid_{x=0,L}, \quad i = 1,2,3. \tag{3.11}$$

Equations (3.10) constitutes a set of linear homogeneous equations of first order in time with constant coefficients. They therefore have solutions of the form:

$$\begin{bmatrix} \varepsilon_1(x,t) \\ \varepsilon_2(x,t) \\ \varepsilon_3(x,t) \end{bmatrix} = e^{\lambda t}\begin{bmatrix} \bar{\varepsilon}_1(x) \\ \bar{\varepsilon}_2(x) \\ \bar{\varepsilon}_3(x) \end{bmatrix}. \tag{3.12}$$

As the Laplacian is the only operator acting on the space coordinates, we choose its eigenfunctions in order to investigate the stability of the system:

$$\begin{aligned} \frac{d^2}{dx^2}\bar{\varepsilon}_1^{(k)}(x) &= -h_k^2\bar{\varepsilon}_1^{(k)}(x) \\ \frac{d^2}{dx^2}\bar{\varepsilon}_2^{(m)}(x) &= -p_m^2\bar{\varepsilon}_2^{(m)}(x) \\ \frac{d^2}{dx^2}\bar{\varepsilon}_3^{(n)}(x) &= -q_n^2\bar{\varepsilon}_3^{(n)}(x), \end{aligned} \tag{3.13}$$

where k, m and n are sets of induces labelling the infinite sets of eigenfunctions and the minus signs in front of h_k, p_m and q_n takes into account that d^2/dx^2 is a dissipative operator having non-positive eigenvalues. The h_k, p_m and q_n are functions of L, γ_i, $i = 1,2,3$, respectively. The applied BCs generate the following equations for the wave vectors:

$$\begin{aligned} (h_k^2 - \gamma_1^2)\sin(h_k L) &= 2h_k L\cos(h_k L) \\ (p_m^2 - \gamma_2^2)\sin(p_m L) &= 2p_m L\cos(p_m L) \\ (q_n^2 - \gamma_3^2)\sin(q_n L) &= 2q_n L\cos(q_n L), \end{aligned}$$

respectively. In order to obtain $h_k(\gamma_1), p_m(\gamma_2)$ and $q_n(\gamma_3)$, these equations must be solved numerically.

By substituting Eqs. (3.12) and (3.13) into Eq. (10), we obtain:

$$\begin{bmatrix} c_1^{(k)} & a_{12} & a_{13} \\ a_{21} & c_2^{(m)} & a_{23} \\ a_{31} & a_{32} & c_3^{(n)} \end{bmatrix} \begin{bmatrix} \bar{\varepsilon}_1^{(k)} \\ \bar{\varepsilon}_2^{(m)} \\ \bar{\varepsilon}_3^{(n)} \end{bmatrix} = \lambda(h_k, p_m, q_n) \begin{bmatrix} \bar{\varepsilon}_1^{(k)} \\ \bar{\varepsilon}_2^{(m)} \\ \bar{\varepsilon}_3^{(n)} \end{bmatrix}, \tag{3.14}$$

where

$$c_1^{(k)} = a_{11} - D_1 h_k^2, \quad c_2^{(m)} = a_{22} - D_2 p_m^2, \quad c_3^{(n)} = a_{33} - D_3 q_n^2.$$

This system has nontrivial solutions provided that the following equation is satisfied:

$$\begin{vmatrix} \lambda - c_1^{(m)} & -a_{12} & -a_{13} \\ -a_{21} & \lambda - c_2^{(m)} & -a_{23} \\ -a_{31} & -a_{32} & \lambda - c_3^{(n)} \end{vmatrix} = 0 \tag{3.15}$$

Depending on the variables $D_i, \gamma_i, a_{ij},\ i,j = 1,2,3$, the frequency λ can be either real or complex which leads in some particular cases to bifurcations. Therefore, in the following we will consider those situations around each uniform steady state separately based on Eq. (3.15).

3.4.2 The analysis of $E_0(0, 0, \xi^{-1}\Delta)$

In this case, $u_1^c = u_2^c = 0$ and $v^c = \xi^{-1}\Delta$. Evaluating a_{ij} at this steady state, we obtain from (3.15) that

$$\begin{vmatrix} \lambda + D_1 h_k^2 + a_1^{-1}\xi^{-1} p_1 \Delta - \alpha_1 & 0 & 0 \\ 0 & \lambda + D_2 p_m^2 + a_2^{-1}\xi^{-1} p_2 \Delta - \alpha_2 & 0 \\ a_1^{-1}\xi^{-1} c_2 \Delta & a_2^{-1}\xi c_2 \Delta & \lambda + D_3 q_n^2 + \xi \end{vmatrix} = 0.$$

Hence

$$\begin{aligned} \lambda_1 &= \alpha_1 - a_1^{-1}\xi^{-1} p_1 \Delta - D_1 h_k^2 \\ \lambda_2 &= \alpha_2 - a_2^{-1}\xi^{-1} p_2 \Delta - D_2 p_m^2 \\ \lambda_3 &= -\xi - D_3 q_n^2. \end{aligned}$$

As a result, we have the following theorem.

Theorem 3.4.4 *For system (3.1), no Turing instability occurs and the diffusion has no effect on the stability of the uniform steady state* $E_0(0;0;\xi^{-1}\Delta)$ *if* $\alpha_1 < a_1^{-1}\xi^{-1}p_1\Delta$ *and* $\alpha_2 < a_2^{-1}\xi^{-1}p_2\Delta$. *However, if* $\alpha_1 > a_1^{-1}\xi^{-1}p_1\Delta + D_1h_k^2$ *or* $\alpha_2 > a_2^{-1}\xi^{-1}p_2\Delta + D_2p_m^2$, *then* $E_0(0;0;\xi^{-1}\Delta)$ *becomes unstable.*

Thoerem 3.4.4 shows that with a fixed wave number, a necessary condition for cancer growth is that α_2 should be sufficiently large with a relatively weak intensity treatment (small $a_2^{-1}p_2$), which coincides with our intuition.

3.4.3 The analysis of $E_1(\hat{u}_1, 0, \hat{v})$

Again, in this case, $u_1^c = \hat{u}_1$, $u_2^c = 0$ and $v^c = \hat{v}$. Evaluating a_{ij} at this steady state gives that

$$\begin{vmatrix} \lambda + D_1h_k^2 - a_{11} & -a_{12} & -a_{13} \\ 0 & \lambda + D_2p_m^2 - a_{22} & 0 \\ -a_{31} & -a_{32} & \lambda + D_3q_n^2 - a_{33} \end{vmatrix} = 0,$$

where

$$a_{11} = \alpha_1(1 - \frac{2\hat{u}_1}{K}) - \frac{a_1p_1\hat{v}}{(a_1+\hat{u}_1)^2}, \quad a_{12} = -\alpha_1r_{12}\hat{u}_1K^{-1}, \quad a_{13} = -\frac{p_1\hat{u}_1}{a_1+\hat{u}_1},$$

$$a_{21} = 0, \quad a_{22} = \alpha_2(1 - \frac{r_{21}\hat{u}_1}{K}) - \frac{p_2\hat{v}}{a_2}, \quad a_{23} = 0,$$

$$a_{31} = -\frac{a_1c_1\hat{v}}{(a_1+\hat{u}_1)^2}, \quad a_{32} = -a_2^{-1}c_2\hat{v}, \quad a_{33} = -[\xi + \frac{c_1\hat{u}_1}{a_1+\hat{u}_1}].$$

Hence

$$\lambda_2 = a_{22} - D_2h_k^2,$$

$$\sigma(\mathrm{A}) = \{\lambda_i \,|\lambda^2 - Tr(\mathrm{A})\lambda + \det(\mathrm{A}) = 0, i = 1,3\},$$

where

$$A = \begin{bmatrix} a_{11} - D_1 h_k^2 & a_{13} \\ a_{31} & a_{33} - D_3 q_n^2 \end{bmatrix}.$$

If $\hat{u}_1 > K/2$, then

$$a_{11} = -\alpha_1(\frac{2\hat{u}_1}{K} - 1) - \frac{a_1 p_1 \hat{v}}{(a_1 + \hat{u}_1)^2} < 0,$$

and

$$\begin{aligned} a_{11}a_{33} - a_{13}a_{31} &= -[\alpha_1(1 - \frac{2\hat{u}_1}{K}) - \frac{a_1 p_1 \hat{v}}{(a_1 + \hat{u}_1)^2}](\xi + \frac{c_1\hat{u}_1}{a_1 + \hat{u}_1}) - \frac{a_1 c_1 p_1 \hat{u}_1 \hat{v}}{(a_1 + \hat{u}_1)^3} \\ &= -\alpha_1(1 - \frac{2\hat{u}_1}{K})(\xi + \frac{c_1\hat{u}_1}{a_1 + \hat{u}_1}) + \frac{p_1 a_1 \Delta\xi}{(a_1 + \hat{u}_1)[a_1\xi + (\xi + a_1)\hat{u}_1]} > 0. \end{aligned}$$

Since $a_{33} < 0$, we have

$$Tr(A) = a_{11} + a_{33} - D_1 h_k^2 - D_3 q_n^2 < 0,$$

$$det(A) = D_1 D_3 h_k^2 q_n^2 - (a_{11} D_3 q_n^2 + a_{33} D_1 h_k^2) + (a_{11}a_{33} - a_{13}a_{31}) > 0.$$

By the Routh-Hurwitz criteria, we have $Re\lambda_i < 0$, $i = 1, 3$. Note that $E_1(\hat{u}_1, 0, \hat{v})$ is locally asymptotically stable if $\alpha_2 < \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2{}^{-1} p_2 \hat{v}$ in the absence of diffusion. Therefore, there no Turing instability occurs under the diffusion case.

Theorem 3.4.5 *For system (3.1), suppose that* $\hat{u}_1 > K/2$, *and* $\alpha_2 \neq \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2{}^{-1} p_2 \hat{v} + D_2 p_m^2$. *Then no Turing instability occurs and the diffusion has no effect on the stability of the uniform steady state* $E_1(\hat{u}_1, 0, \hat{v})$ *provided that* $\alpha_2 < \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2{}^{-1} p_2 \hat{v}$. *However, if* $\alpha_2 > \alpha_2 K^{-1} r_{21}\hat{u}_1 + a_2^{-1} p_2 \hat{v} + D_2 p_m^2$, *then* $E_1(\hat{u}_1, 0, \hat{v})$ *becomes unstable and the cancer cells begin to grow and eventually win the competition with the normal cells.*

Comparing with *Theorem* 3.3.4 in the no diffusion case, *Theorem* 3.4.5 shows that the diffusion has no effect on the stability of the uniform steady state $E_1(\hat{u}_1, 0, \hat{v})$, and there is no Turing instability to occur in the diffusion case. However, the survival of populations will also depend on the space along with those factors (see *Theorem* 3.3.4) included in the no diffusion case. The simulation of our models demonstrates that small diffusion does benefit the survival of both populations in such a case (see *Figure* 3.4).

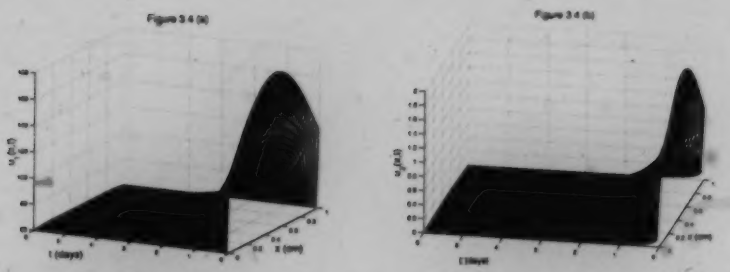

Figure 3.4: Distribution of solutions in space and time for model (3.1) with the same parameters as in the no diffusion case of *Figure* 3.1 along with, $D_1 = 0.001, D_2 = 0.02, D_3 = 0.03, u_1(x,0) = 60(2+\sin(\pi x)), u_2(x,0) = 1+\sin(\pi x), v(x,0) = 5(2+\sin(\pi x))$. (a) normal cells, (b) cancer cells. *Figure*3.4 shows that (1) the uniform steady sate $E_1(\hat{u}_1, 0, \hat{v})$ is locally asymptotically stable and the diffusion has no effect on the stability and no Turing instability occurs, (2) small diffusion does benefit the survival of populations on the boundary and the inside of the diffusion region under the treatment (compare to *Figure*3.1), (3) due to the heavy dose of drugs, all cancer cells including those on the boundary eventually are driven to extinction from initial levels, and normal cells win the competition with cancer cells and eventually approach the carrying capacity.

3.4.4 The analysis of $E_2(0, \tilde{u}_2, \tilde{v})$

In this case, $u_1^c = 0$, $u_2^c = \tilde{u}_2$ and $v^c = \tilde{v}$. Evaluating a_{ij} at this point, we obtain:

$$\begin{vmatrix} \lambda + D_1 h_k^2 - b_{11} & 0 & 0 \\ -b_{21} & \lambda + D_2 p_m^2 - b_{22} & -b_{23} \\ -b_{31} & -b_{32} & \lambda + D_3 q_n^2 - b_{33} \end{vmatrix} = 0,$$

where

$$b_{11} = a_1 - a_1 K^{-1} r_{12} \tilde{u}_2 - a_1^{-1} p_1 \tilde{v}, \quad b_{12} = 0, \quad b_{13} = 0,$$

$$b_{21} = -\alpha_2 K^{-1} r_{21} \tilde{u}_2, \quad b_{22} = \alpha_2 (1 - \frac{2\tilde{u}_2}{K}) - \frac{a_2 p_2 \tilde{v}}{(a_2 + \tilde{u}_2)^2}, \quad b_{23} = -\frac{p_2 \tilde{u}_2}{a_2 + \tilde{u}_2},$$

$$b_{31} = -a_1^{-1} c_1 \tilde{v}, \quad b_{32} = -\frac{a_2 c_2 \tilde{v}}{(a_2 + \tilde{u}_2)^2}, \quad b_{33} = -[\xi + \frac{c_2 \tilde{u}_2}{a_2 + \tilde{u}_2}].$$

Hence

$$\lambda_1 = b_{11} - D_1 h_k^2,$$

$$\sigma(B) = \{\lambda_i \,|\lambda^2 - Tr(B)\lambda + \det(B) = 0, i = 2,3\},$$

where

$$B = \begin{bmatrix} b_{22} - D_2 p_m^2 & b_{23} \\ b_{32} & b_{33} - D_3 q_n^2 \end{bmatrix}.$$

Similarly, if $\tilde{u}_2 > K/2$, then we have

$$Tr(B) = b_{22} + b_{33} - D_2 p_m^2 - D_3 q_n^2 < 0\,,$$

$$\det(B) = D_2 D_3 p_m^2 q_n^2 - (b_{22} D_3 q_n^2 + b_{33} D_2 p_m^2) + (b_{22} b_{33} - b_{32} b_{23}) > 0\,.$$

Theorem 3.4.6 *For system (3.1), suppose that* $\tilde{u}_2 > K/2$, *and* $\alpha_1 \neq \alpha_1 K^{-1} r_{12} \tilde{u}_2 + a_1^{-1} p_1 \tilde{v} + D_1 h_k^2$. *Then no diffusive instability occurs and the diffusion is harmless to the stability of the uniform steady state* $E_2(0, \tilde{u}_2, \tilde{v})$ *provided* $\alpha_1 < \alpha_1 K^{-1} r_{12} \tilde{u}_2 + a_1^{-1} p_1 \tilde{v}$. *However, if* $\alpha_1 > \alpha_1 K^{-1} r_{12} \tilde{u}_2 + a_1^{-1} p_1 \tilde{v} + D_1 h_k^2$ *then* $E_2(0, \tilde{u}_2, \tilde{v})$ *is unstable and the normal cells will eventually win the competition with the cancer cells under the chemotherapy treatment.*

Comparing with *Theorem* 3.3.6 in the no diffusion case, *Theorem* 3.4.6 shows that the diffusion has no effect on the stability of the uniform steady state $E_2(0, \tilde{u}_2, \tilde{v})$, and no Turing instability occurs in the diffusion case. However, the survival of cell populations will also depend on the space along with those factors (see *Theorem* 3.3.6) included in the no diffusion case. The simulation of our models demonstrates that small diffusion does benefit the survival of both cell populations in such a case (see *Figure* 3.5).

3.5 Numerical results

In order to perform the numerical simulations of system (3.1) and (3.2), we impose some conditions based both on the analytical results and on some physiological arguments:

a) $\alpha_2 > \alpha_1$ (cancer cells grow faster than normal cells).

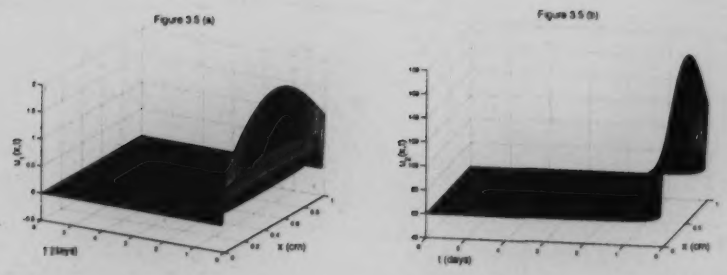

Figure 3.5: Distribution of solutions in space and time for model (3.1) with the same parameters as in the no diffusion case of *Figure* 3.2 along with, $D_1 = 0.001, D_2 = 0.02, D_3 = 0.03, u_1(x,0) = 60(2+\sin(\pi x)), u_2(x,0) = 1+\sin(\pi x), v(x,0) = 5(2+\sin(\pi x))$. (a) normal cells, (b) cancer cells. *Figure*3.5 shows that (1) the uniform steady sate $E_2(0,\tilde{u}_2,\tilde{v})$ is locally asymptotically stable and the diffusion has no effect on the stability and no Turing instability occurs, (2) small diffusion does benefit the survival of cell populations on the boundary and the inside of the diffusion region under the treatment (compare to *Figure*3.2), (3) due to the small dose of drugs, cancer cells eventually win the competition with normal cells and grow to approach the carrying capacity.

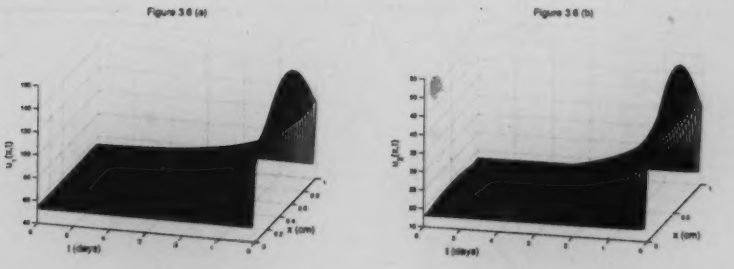

Figure 3.6: Distribution of solutions in space and time for model (3.1) with the same parameters as in the no diffusion case of *Figure* 3.3 along with, $D_1 = 0.0001, D_2 = 0.002, D_3 = 0.003, u_1(x,0) = 53(2+\sin(\pi x)), u_2(x,0) = 18.1(2+\sin(\pi x)), v(x,0) = 5(2+\sin(\pi x))$. (a) normal cells, (b) cancer cells. *Figure* 3.6 demonstrates that (1) the normal cells grow and peak at a level which is far higher than that for the abnormal cells, which is due to the weakening effects of cancer inhibition and regeneration of the normal cells, and (2) the heavy drug dosage ultimately causes damage to regrowth and proliferative capabilities of the cancer cells, and keeps it at a lower level than that of normal cells.

b) $p_2 >> p_1$ (the drug is more potent against the cancer cells than against the normal cells).

c) $c_2 >> c_1$ (a consequence of the above item).

d) the hypotheses of *Theorems* 3.3.1 and 3.3.2 which guarantee the existence of E_1 and E_2 are satisfied.

Also the initial condition is such that: $u_1^0 > u_2^0$ (in general), i.e. the cancer is initially not too advanced.

In the no diffusion case, *Figure* 3.1 shows that the boundary equilibrium $E_1(60.0, 0, 5.0)$ is locally stable. Initially, the cancer cells grow but eventually decrease and are driven to extinction. This is due to the heavy dose of chemotherapy drugs, which inhibits the proliferative capacities of the cancer cells and causes damage to the cancer growth.

In the no diffusion case, *Figure* 3.2 shows that solutions for model (3.2) approach $E_2(0, 60.0, 5.0)$ if the treatment intensity is weak (small values of ${a_2}^{-1}p_2$ and/or $\xi^{-1}\Delta$). Here other parameters and initial conditions are the same as in *Figure* 3.1 except $p_2 = 0.01$. From *Figure* 3.2 it is easy to see that (1) the normal cells grow at the beginning due to their large initial size but eventually lose the competition with the cancer cells and decrease to zero due to the weak intensity treatment(small p_2), and (2) the cancer cells accumulate persistently at the beginning and take about 20 days to dominate the normal cells. This is due to the weak intensity of the treatment. *Figure* 3.3 shows that system (2) is uniformly persistent and the interior equilibrium $E_3(53.0, 18.1, 5.0)$ is locally stable. Here also the drug is selectively lethal to the cancer cells and controls them at a lower level than the normal cells.

In the presence of diffusion, *Figure* 3.4 shows the distribution of solutions in space and time for model (3.1) with the same parameters as in the no diffusion case of *Figure* 3.1 along with, $D_1 = 0.001, D_2 = 0.02, D_3 = 0.03, u_1(x, 0) = 60(2 + \sin(\pi x)), u_2(x, 0) = 1 + \sin(\pi x), v(x, 0) = 5(2 + \sin(\pi x))$. From *Figure*3.4 we can see that (1) the uniform steady sate $E_1(\hat{u}_1, 0, \hat{v})$ is locally asymptotically stable and the diffusion has no effect on the stability and no Turing instability occurs, (2) small diffusion does benefit the survival of populations on the boundary and the inside of the diffusion region under the treatment

(compare to *Figure*3.1), (3) due to the heavy dose of drugs, all cancer cells including those on the boundary eventually are driven to extinction from initial levels, and normal cells win the competition with cancer cells and eventually approach the carrying capacity.

In the diffusion case, *Figure* 3.5 shows the distribution of solutions in space and time for model (3.1) with the same parameters as in the no diffusion case of *Figure* 3.2 along with, $D_1 = 0.001, D_2 = 0.02, D_3 = 0.03, u_1(x,0) = 60(2+\sin(\pi x)), u_2(x,0) = 1+\sin(\pi x), v(x,0) = 5(2+\sin(\pi x))$. From *Figure*3.5 we can see that (1) the uniform steady sate $E_2(0,\tilde{u}_2,\tilde{v})$ is locally asymptotically stable and the diffusion has no effect on the stability and no Turing instability occurs, (2) small diffusion does benefit the survival of cell populations on the boundary and the inside of the diffusion region under the treatment (compare to *Figure*3.2), (3) due to the small dose of drugs, cancer cells eventually win the competition with normal cells and grow to approach the carrying capacity. *Figure* 3.6 shows the distribution of solutions in space and time for model (3.1) with the same parameters as in the no diffusion case of *Figure* 3.3 along with, $D_1 = 0.0001, D_2 = 0.002, D_3 = 0.003, u_1(x,0) = 53(2+\sin(\pi x)), u_2(x,0) = 18.1(2+\sin(\pi x)), v(x,0) = 5(2+\sin(\pi x))$.

Finally, in the diffusion case, *Figure* 3.6 demonstrates that (1) the normal cells grow and peak at a level which is far higher than that for the abnormal cells, which is due to the weakening effects of cancer inhibition and regeneration of the normal cells, and (2) the heavy drug dosage ultimately causes damage to regrowth and proliferative capabilities of the cancer cells, and keeps it at a lower level than that of normal cells.

Comparing with *Theorem* 3.3.4 in the no diffusion case, *Theorem* 3.4.5 shows that the diffusion has no effect on the stability of the uniform steady state $E_1(\hat{u}_1,0,\hat{v})$, and there is no Turing instability to occur in the diffusion case. However, the survival of populations will also depend on the space along with those factors (see *Theorem* 3.3.4) included in the no diffusion case. The simulation of our models demonstrates that small diffusion does benefit the survival of both populations in such a case (see *Figure* 3.4).

Comparing with *Theorem* 3.3.6 in the no diffusion case, *Theorem* 3.4.6 shows that the diffusion has no effect on the stability of the uniform steady state $E_2(0,\tilde{u}_2,\tilde{v})$, and no Turing instability occurs in the diffusion case. However, the survival of cell populations

will also depend on the space along with those factors (see *Theorem* 3.3.6) included in the no diffusion case. The simulation of our models demonstrates that small diffusion does benefit the survival of both cell populations in such a case (see *Figure* 3.5).

3.6 Discussion

The three most important steady states of our model from a physiological point of view are E_1, E_2 and E_3. E_1 represents a cancer free state, and of course the most desirable result would be to have E_1 globally asymptotically stable. E_2 represents a state which is exclusively cancerous and is a lethal state for the individual. E_3 represents a state where normal and cancer cells exist simultaneously.

We are able to obtain analytic criteria for E_1 to be locally asymptotic stable, but not globally stable. Numerically, we can show that if treated with a heavy dose of drugs (big value of p_2), solutions may approach E_1 (*Figure* 3.1). However, solutions may approach E_2 (*Figure* 3.2) if the treatment intensity is weak (small values of $a_2^{-1}p_2$ and/or $\xi^{-1}\Delta$), and may approach E_3 (*Figure* 3.3) if the treatment intensity is strong (higher values of $a_2^{-1}p_2$ and/or $\xi^{-1}\Delta$). This demonstrates an equi-asymptotical stability in the large for E_3. Also the region of stability of E_1 is found numerically to increase with higher treatment levels. On the other hand, we show that it is possible to choose parameters and initial values so that solutions of system (3.1) approach a positive state E_3 with the cancer level small. In a bounded space region, we find numerically that diffusion has no effect on the stability of constant solutions and no Turing instability occurs. If the treatment is strong enough, then solutions of system (3.1) approach the uniform steady state E_1 (*Figures* 3.4) and the drugs kill all cancer cells. In the case of a weak intensity treatment, we find normal cells lose the competition with cancer cells and all cells including those on the boundary are driven to extinction (*Figure* 3.5 (a)). However, in such a situation (weak intensity treatment) cancer cells have the growth advantage over normal cells and eventually win the competition with all normal cells and approach the carrying capacity eventually (*Figure* 3.5 (b)). Numerically, it is also possible to choose parameters and initial values so that solutions of system (1) approach a positive state E_3 with the cancer level small in the diffusion case (*Figure* 3.6) under a reasonable treatment.

In a population system, diffusion or dispersal exists in many instances. However, in some systems, when diffusions are considered, the stability of the corresponding ODE systems may be changed. Hence one of the purpose of this work is to fully understand just what features of reaction-diffusion systems are necessary and sufficient for Turing instabilities and compare the dynamics of our model in the case of no diffusion to the diffusion case. Unfortunately, Turing instability does not occur in the systems considered here. However, we prove that each uniform steady state is unique for the system and asymptotically stable in both cases, which means that in this kind of a system, the diffusion does not change the stability. However, our numerical solutions show that a small diffusion may benefit the survival of all cell populations.

Finally, with respect to clinical advantage, we point out how our results may be useful to leukemia treatment. For those situations in which our models may apply, the theorems identify which combination of coefficients, i.e. sufficiently high or low values would lead to low levels of cancer, or elimination altogether. It is known [92] that different leukemias can be treated with various successes (or failures), and our results may be used to help in improving the successes (i.e. the rate of success or length of remission time).

4

A Mathematical Model of Chemotherapy Treatment with Chronic Myeloid Leukemia

4.1 Introduction

Hematopoietic stem cells are generally characterized by three properties: they are capable of dividing and renewing themselves for long periods of time; the process of differentiation is not complete; and after dividing, each daughter cell either remains a stem cell or proceeds to a terminal differentiation in order to form different types of blood cells throughout the body such as leukocytes (white blood cells), erythrocytes (red blood cells), lymphocytes and platelets [25]. B and T leukocytes form part of the immune response and serve to prevent infections. They travel in the blood stream, but also can pass into tissues surrounding the circulatory system. Other cells that circulate with the leucocytes, are erythrocytes which contain hemoglobin for transport of oxygen throughout the body, and platelets which participate in the process of hemostasis(or blood clotting).

Chronic myeloid leukemia(CML), also known as granulocytic leukemia, chronic myelogenous leukemia, and chronic myelocytic leukemia, is a clonal stem cell disorder that begins as an indolent disease in which the myeloid lineages in the bone marrow and blood gradually expand. The hallmark of CML is the Philadelphia chromosome(22q-)

resulted from a reciprocal translocation that also involves chromosome 9. The reciprocal translocation $t(9,22)$ generates two novel fusion genes: BCR-ABL on the derivative 22q- chromosome, and ABL-BCR on chromosome 9q+ [22,51]. The ABL gene product is a protein tyrosine kinase, and the fusion protein BCR-ABL has constitutive kinase activity that deregulates signal transduction pathways, causing abnormal cell cycling, inhibition of apoptosis, and increased proliferation of immature cells. BCR-ABL is very important because in patients with CML, the clonal expansion of hematopoietic stem cells express this unique fusion gene. Moreover, continued expression of BCR-ABL is required for sustained proliferation of leukemic cells [22,43,50,51].

From the view point of cytokinetics, it is generally believed that CML develops when a single, pluripotential, hematopoietic stem cell acquires a Ph chromosome carrying the BCR-ABL gene, which confers on its progeny a proliferative advantage over normal hematopoietic elements and thus allows the Ph-positive clone gradually to displace residual normal hematopoiesis [25]. This competitive growth advantage of abnormal stem cells usually gives rise to a malignant proliferation and subsequently, to the relative dominance of the abnormal stem cell population. Frequently, the abnormal cells do not differentiate at a sufficiently high rate to form healthy levels of white and red blood cells. This results in anemia and in a weakened immune system, vulnerable to infections [20]. Moreover, CML stem cells seem to survive longer than their normal counterparts as a result of defective apoptotic response to stimuli that would otherwise lead to physiologic cell death.

Dynamically, CML progresses through three phases: the chronic phase, the acceleration phase, and the acute phase. The mechanisms for the evolution of the massive hyperplasia and for the blastic crisis from CML are poorly understood. The most generally accepted hypothesis proposes that this progression is due to the development of genetic instability in the leukemic cells. In particular, the last two phases of the disease are believed to reflect different, discrete genetic events. Such events remain undefined as yet, and the causal significance of observed genetic aberrations is not clear.

In humans and mice, hematopoietic stem cells are the only normal progenitors that renew themselves [2,4,23,57,67,73,78,103] and therefore, they are widely considered to be the only cells in the marrow in which preleukemic changes can accumulate, whether by

genetic or epigenetic means. However, it is also possible that a downstream progenitor can acquire self-renewal capacity[53,67,81,87,88] and the deregulation of self-renewal pathways in these progenitors, which are normally tightly regulated in hematopoietic stem cells [2,23,57,67,73,78,88,103,108] has been recognized as an important step in leukemic progression. Recent work (Jamieson et al [52]) shows that the progression of CML to blast crisis is supported by self-renewing leukemic progenitor cells. Unlike normal granulocyte-macrophage progenitors, CML granulocyte-macrophage progenitors form self-renewing myeloid colonies and the progenitor pool from patients with CML in blast crisis, rather than the pool of hematopoietic stem cells, is expanded, generates BCR-ABL and has elevated levels of nuclear β-cantenin as compared with the levels in progenitors from normal marrow, increasing their proliferative and self-renewal capacity and possibly allowing them to become leukemic stem cells, thus giving rise to the progression to blast crisis [52]. Here, β-cantenin is cytoplasmic protein that has important structural and signaling functions. Expressing β-cantenin usually leads to an enhanced ability of self-renewal of hematopoietic stem cells. Abnormalities in the regulation of structural and signaling functions of β-cantenin gives rise to tumorigenesis [52].

Working on the haematopoietic stem cell population (HSC), Mackey [65] proposed a standard G_0 model for the cell cycle in order to calculate the steady state parameters characterizing the HSC populations, such as the differentiation rate, the rate of cell re-entry from G_0 back into the proliferative phase, and the rate of apoptosis. The purpose of [65] is to understand how the HSC population carries out the cellular production over the course of a lifetime and thus the kinetics of HSC populations. In this chapter, we work on a downstream compartment, granulocyte-macrophage progenitor compartment in which we assume that the cells obtain a self-renewal capacity and the progenitor cells go into a cell cycle with a similar standard G_0 model properties as in [65]. Due to the lack of better knowledge about the cell kinetics in this compartment, we do not know what specific function forms the model will take in this compartment. Based on the bio-medical work in [52], a general formulation with self-renewal properties is proposed to mathematically study the dynamical progression of the disease. Our interest here is to formulate a plausible explanation of the transition from the seeming stable chronic phase

to the unstable acceleration phase and ultimately, to the rapidly changing acute phase.

Finally, based on all the qualitative behaviors of the model, a continuous treatment for CML is considered. Herein, our model is significantly different from [65] in that more general functions and treatment are included. The ultimate role of our mathematical modelling in cancer treatment is to provide a more rational basis for experimental design of the anti-cancer drugs and to make qualitative predictions with regard to the dynamic evolution of the disease based on the cytokinetic parameters of the patient and the drug parametric configuration. In cancer treatment today, four types of treatment are most commonly used in efforts to obtain long-term periods of disease-free remission. These include surgery, radiotherapy, chemotherapy and immunotherapy. Allogeneic bone marrow transplantation can cure chronic-phase CML in up to 70 percent of patients, but the use of this procedure is limited by the toxicity of the treatment, the risk of graft-versus-host disease, and the lack of suitable donors for many patients. Cancer chemotherapy treatment now has demonstrated a definite capacity for controlling disseminated metastatic cancer and is therefore widely used (Dorr and Von Ho [24], Frei [37], Liotta [63], Perry [84]). In cancer chemotherapy, anti-neoplastic drugs are designed to selectively destroy or inhibit the proliferative activity of cancer cells while the normal cells are affected to a lesser extent (Dorr and Von Ho [24], Frei [37]). Recent studies show that up to 80 percent of patients enter a period of complete cytogenetic remissions when treated with imatinib mesylate(called Gleevec), a new ABL-specific tyrosine kinase inhibitor that specifically blocks the enzymatic action of the BCR-ABL fusion proteins [45]. The introduction into clinical practise of such an inhibitor promises to be a major contribution to the management of CML and may also prove to be the lead agent that ushers in an era of success with molecularly targeted therapy for other leukemias, lymphomas, and cancers. Interferon alfa therapy also extends survival by one to two years and can reduce the number of cells with the Philadelphia chromosome [82]. Combined treatment with interferon alfa and cytarabine may have further benefits, and many view it as the gold standard of therapy. It is within this context that our studies of chronic myeloid leukemia and its corresponding chemotherapy treatment may be significant.

The organization of this chapter is as follows. In the next section, we develop our model.

In section 4.3 we discuss the invariance of nonnegativity, boundedness of solutions, nature of equilibria, and their stabilities in the no treatment case. In the section that follows we look at the continuous treatment case: we discuss the existence and local stability of relevant equilibria, and check the effects of the time delay on the stability of solutions. These are done both analytically and numerically. In section 4.5 we give some numerical examples to illustrate our results. Out final section contains a discussion.

4.2 The model

In order to better understand the standard G_0 model properties in [65], we make the following assumptions. The stem cells progress through a multi-staged system. Steps to model such a population are as follows:

1) The granulocyte-macrophage stem cells constitute a population (compartment GM) with its own feedback mechanism controlling population size. This means that at any given time, the population of stem cells is evaluated and if this population is greater than a certain threshold, future production will be reduced. Conversely, if the population lies below the threshold, more cells will begin a process of self-renewal. This mechanism serves to maintain the stem cell population at some optimal level while smoothing out both positive and negative perturbations from this level. The process of self-replication, though, takes a non-trivial amount of time. Hence, when new cells are entering the system, they are entering based on slightly outdated information. As such, certain values for the delay most likely exist which would give rise to an instability in this system leading to blast crisis.

2) When the population size reaches the "normal" state (no cells removed from the population) the cells are in a state of dormancy with respect to growth, that is, the cells neither proliferate nor initiate any further cellular differentiation and just remain in their current compartment.

3) When a number of cells is removed from the population(at a rate $\delta(N)$, with N representing the number of cells) the feedback mechanism triggers an equal number from the remaining cells.

4) The triggered cells "emit" a signal which may be interpreted as "message received and understood".

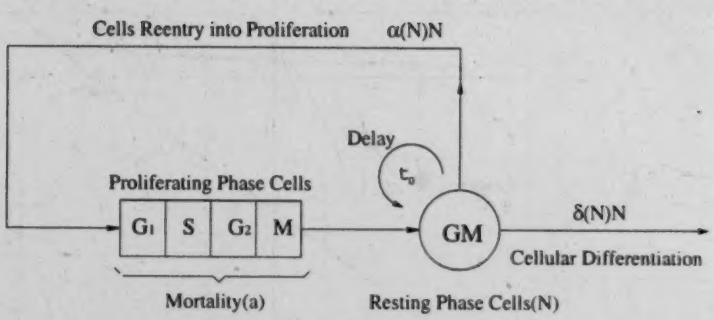

Figure 4.1: Based on *Figure* 3.6 in Neiman [77], the GM model for cell growth shows how cells may either remain in the GM resting phase, go through a process of self-renewal to reproduce cells, or begin a differentiation process to form different types of cells.

5) The feedback mechanism ceases to create further cells.

6) The triggered cells begin a self-renewal process (at a rate $\alpha(N)$)involving four phases: G_1, S, G_2, and M phases. Thus the population size is returned to normal.

The stem cell population has, however, the particular characteristics of never in fact reaching its "normal" size (and with a dormancy state for all its cells) due to the existence of a continuous removal of cells from the population by an exogenous mechanism [77]. Therefore, in the physiological steady state of haemopoiesis a balance should exist, in which, a physiological mechanism is removing (at a rate $\delta(N)$) a certain proportion of stem cells from the stem cell population, and therefore, the positive feedback control for the population size triggers a similar proportion of stem cells moving into the cell cycle (at a rate $\alpha(N)$). Hence, after a time delay τ, two cells re-enter the compartment as a result of one cell self-renewing. Some cells will die (at a rate a) during this proliferation process. The model is illustrated in *Figure* 4.1.

Now let $x(t)$ represent the concentration of normal cells in the GM phase, $y(t)$ the concentration of leukemia cells, and $u(t)$ the concentration of chemotherapy agents. The model then takes the form

$$\begin{aligned}
\dot{x}(t) &= 2(1-a_1)x_{\tau_1}\alpha_1(x_{\tau_1},y_{\tau_1}) - x\alpha_1(x,y) - \delta_1 x(t) - p_1(x)w(u) \\
\dot{y}(t) &= 2(1-a_2)y_{\tau_2}\alpha_2(x_{\tau_2},y_{\tau_2}) - y\alpha_2(x,y) - \delta_2 y(t) - p_2(y)w(u) \\
\dot{u}(t) &= \Delta - [\gamma + \eta_1 p_1(x) + \eta_2 p_2(y)]w(u),
\end{aligned} \tag{4.1}$$

with initial conditions

$$x(t) = \phi_1(t) \geq 0,\ y(t) = \phi_2(t) > 0,\ u(0) = u_0,\ t \in [-\tau, 0], \tau = max\{\tau_1, \tau_2\},$$

where τ_1 and τ_2 are the delays for the normal and cancer cells, respectively; $x_{\tau_1} = x(t-\tau_1)$, $y_{\tau_2} = y(t-\tau_2)$.

a_1, a_2 are the respective cell mortality rates of normal and abnormal cells in a cell cycle period.

α_1, α_2 represent the self-renewal growth rates of normal and abnormal cells, respectively.

δ_1, δ_2 are the respective differentiation rates.

p_1, p_2 represent the cell-killing rates per unit agent of the chemotherapy.

η_1, η_2 represent the combination rates of the chemotherapy agents with the cells.

w is the concentration dependent chemotherapy effect.

γ is the loss rate of poison for chemotherapy agents.

Δ is the rate of continuous constant infusion of chemotherapy agents.

Specifically we assume the following properties for the defined functions.

(A_1): According to the negative feedback properties for controlling cell population size and the competing properties between both cell populations, the growth rate is diminished by increasing the number of either cell population. This leads to the condition

$$\frac{\partial \alpha_1(x,y)}{\partial x} < 0,\ \frac{\partial \alpha_1(x,y)}{\partial y} < 0,\ \frac{\partial \alpha_2(x,y)}{\partial x} < 0,\ \frac{\partial \alpha_2(x,y)}{\partial y} < 0.$$

(A_2): Both cell populations should grow if they are very small. Hence

$$\alpha_1(0,0) > 0,\ \alpha_2(0,0) > 0.$$

(A_3): It is supposed that there are proliferative limits for each cell population, which could occupy the space and be adequately supported by the environment in the absence of the competing cell population. This is tantamount to supposing that there exist K_1, K_2 such that

$$\alpha_1(K_1,0) + K_1\frac{\partial \alpha_1(K_1,0)}{\partial x} = 0, \quad \alpha_2(0,K_2) + K_2\frac{\partial \alpha_2(0,K_2)}{\partial y} = 0.$$

(A_4): $p_i(0) = 0$, $p_1'(x) > 0$ for $x > 0$, $p_2'(y) > 0$ for $y > 0$. Further $p_2'(0) > p_1'(0)$ due to the selectivity of the the chemotherapy agent.

(A_5): $w(0) = 0$, $w'(u) > 0$. Further $\lim_{u\to+\infty} w(u) = \bar{w} < +\infty$. The existence of $\bar{w}$ is due to empirical observations of the effect of body enzymes on chemotherapy agents(Agur et al.[1], Curt and Collins [21], Shargel and Yu [94]). We assume that the chemotherapy agent is initially zero at time $t = 0$.

At this point we will establish two important properties of solutions to system (4.1).

Theorem 4.2.1 *All solutions of system (4.1) with positive initial values remain positive.*

Proof. Since $\dot{u}(0) = \Delta > 0$, no solution $u(t)$ of (4.1) with $u(t) > 0$ can become zero. The nonnegativity of $x(t)$ and $y(t)$ can be proved by induction. Assume that $(x(t), y(t)) \geq 0$ for $t \in [(n-1)\tau, n\tau]$. Consider the following initial value problem

$$\begin{aligned} \dot{v}_1(t) &= -v_1(t)(\alpha_1(v_1, v_2) + \delta_1 + q_1(v_1)w(u)) \\ \dot{v}_2(t) &= -v_2(t)(\alpha_2(v_1, v_2) + \delta_2 + q_2(v_2)w(u)), \end{aligned} \tag{4.2}$$

with initial value

$$v_1(n\tau) = x_{n\tau},\ v_2(n\tau) = y_{n\tau},\ t \in [n\tau, (n+1)\tau].$$

It is obvious that $(v_1(t), v_2(t))$ is nonnegative for $(x_{n\tau}, y_{n\tau}) \geq 0$. Hence $v_i(t - \tau_i) \geq 0$. Now one can look at (4.2) and notice that

$$\begin{aligned} 2(1-a_1)x_{\tau_1}\alpha_1(x_{\tau_1}, y_{\tau_1}) - x(t)\alpha_1(x, y) - \delta_1 x(t) - x(t)q_1(x)w(u) &\geq \\ -x(t)\alpha_1(x, y) - \delta_1 x(t) - x(t)q_1(x)w(u); \\ 2(1-a_2)y_{\tau_2}\alpha_2(x_{\tau_2}, y_{\tau_2}) - y(t)\alpha_2(x, y) - \delta_2 y(t) - y(t)q_2(y)w(u) &\geq \\ -y(t)\alpha_2(x, y) - \delta_1 y(t) - y(t)q_2(y)w(u), \end{aligned}$$

where we have set $p_i(v) = vq_i(v)$. Therefore,

$$\begin{aligned} \dot{x}(t) &\geq -v_1(t)(\alpha_1(v_1, v_2) + \delta_1 + q_1(v_1)w(u)) \\ \dot{y}(t) &\geq -v_2(t)(\alpha_2(v_1, v_2) + \delta_2 + q_2(v_2)w(u)),\ t \in [n\tau, (n+1)\tau]. \end{aligned} \tag{4.3}$$

It follows that $\dot{x}(t) \geq \dot{v}_1(t)$, $\dot{y}(t) \geq \dot{v}_2(t)$ with initial values $v_1(n\tau) = x(n\tau)$, $v_2(n\tau) = y(n\tau)$. Moreover, the solution of (4.2) is nonnegative because $v_1(n\tau) = x(n\tau) \geq 0$, $v_2(n\tau) = y(n\tau) \geq 0$. This implies from comparison theory that $x(t) \geq v_1(t)$, $y(t) \geq v_2(t)$ for $t \in [n\tau, (n+1)\tau]$. Hence $x(t) \geq 0$, $y(t) \geq 0$. Notice that $x(t) = \phi_1(t) \geq 0$, $y(t) = \phi_2(t) > 0$ for all $t \geq 0$. It follows that $x(t) \geq 0$, $y(t) > 0$ for all $t \geq 0$.

Theorem 4.2.2 *System* (4.1) *is dissipative provided that there exists* $M_1 > 0$, $M_2 > 0$ *such that* $\|\phi_1\| \leq M_1$, $\|\phi_2\| \leq M_2$.

Proof. Since the initial conditions are nonnegative, then so are the solutions. From (4.1) we have

$$\begin{aligned} \dot{x}(t) &\leq 2(1-a_1)x_{\tau_1}\alpha_1(x_{\tau_1}, y_{\tau_1}) - \delta_1 x(t) \\ &\leq 2(1-a_1)x_{\tau_1}\alpha_1(x_{\tau_1}, 0) - \delta_1 x(t) \\ &\leq 2(1-a_1)K_1\alpha_1(K_1, 0) - \delta_1 x(t), \end{aligned}$$

that is,

$$\dot{x}(t) \leq \xi_1 - \delta_1 x(t), \quad \xi_1 = 2(1-a_1)K_1\alpha_1(K_1, 0) > 0.$$

By using the "variation of constants" formula for the inequality and standard comparison theory, we obtain

$$x(t) \leq x(t_0)e^{-\delta_1(t-t_0)} + \frac{\xi_1}{\delta_1}(1 - e^{-\delta_1(t-t_0)}).$$

Passing to the limit superior in both sides, we get

$$\limsup_{t\to\infty} x(t) \leq \frac{\xi_1}{\delta_1}.$$

Similarly, we have

$$\dot{y}(t) \leq \xi_2 - \delta_2 y(t), \quad \xi_2 = 2(1-a_2)K_2\alpha_2(0, K_2) > 0.$$

Again, with the help of the " variation of constants" formula for the inequality and standard comparison theory, we obtain

$$\limsup_{t\to\infty} y(t) \leq \frac{\xi_2}{\delta_2}.$$

Note that from (4.1) we have

$$\begin{aligned} \dot{u}(t) &\leq \Delta - \gamma w(u) \\ &\leq \Delta - \bar{\gamma} u(t), \end{aligned}$$

which gives

$$\limsup_{t\to\infty} u(t) \leq \bar{\gamma}^{-1}\Delta,\ \bar{\gamma} = \max\{\gamma\hat{w}(u)\},\ w(u) = u(t)\hat{w}(u).$$

Now let $\bar{M}_i = \max\{M_i, \xi_i/\delta_i\}$. Then the region $\Re = \{(x,y,u) \in R^3_+ : 0 \leq x(t) \leq \bar{M}_1, 0 \leq y(t) \leq \bar{M}_2, 0 \leq u(t) \leq \bar{\gamma}^{-1}\Delta\}$ is an attracting invariant region proving the property. □

Model (4.1) is analyzed throughout the remainder of this chapter. However, before doing so, we need to consider the interaction of normal and cancer cells when there is no treatment. This is done in the next section.

4.3 The no treatment case

In this section we consider the case where there is no treatment for CML, i.e. $u = 0$ for all $t \geq 0$. Our model then takes the form

$$\begin{aligned} \dot{x}(t) &= 2(1-a_1)x_{\tau_1}\alpha_1(x_{\tau_1}, y_{\tau_1}) - x\alpha_1(x,y) - \delta_1 x(t) \\ \dot{y}(t) &= 2(1-a_2)y_{\tau_2}\alpha_2(x_{\tau_2}, y_{\tau_2}) - y\alpha_2(x,y) - \delta_2 y(t), \end{aligned} \tag{4.4}$$

with initial conditions

$$x(t) = \phi_1(t) \geq 0,\ y(t) = \phi_2(t) > 0, t \in [-\tau, 0].$$

System (4.4) has a trivial equilibrium $E_0(0,0)$. Two boundary equilibria are $E_1(\bar{x}, 0)$, $E_2(0, \bar{y})$. It is easy to prove that they exist uniquely provided that $\delta_1 < (1-2a_1)\alpha_1(0,0)$ and $\delta_2 < (1-2a_2)\alpha_2(0,0)$, respectively. Finally the possible interior equilibrium is $E_3(x^*, y^*)$, but sufficient conditions for its existence are not easily obtained. In the final section, we will present some numerical examples to illustrate cases when this equilibrium exists.

4.3.1 Linear stability

In order to examine the stability of the boundary steady states, we employ *Mikhailov's theorem* [29] quoted below.

Theorem 4.3.1 *If $Q(z)$ has no zeros on the imaginary axis, then Q is stable (i.e. a trivial solution $x = 0$ to the linear system of delay differential equations with the characteristic quasi-polynomial equal to Q is asymptotically stable) if and only if $\Delta = \frac{n_0\pi}{2}$, where $\Delta = \Delta_{\omega\in[0,+\infty)} arg Q(i\omega)$, i.e. Δ denotes the change of argument of the vector $Q(i\omega)$ in the positive direction of the complex plane as ω increases from 0 to $+\infty$.*

First, we linearize system (4.4) about a general point (v_1, v_2) and obtain

$$\begin{aligned}\dot{x}(t) &= 2(1-a_1)c_1(x_{\tau_1}-v_1)+2(1-a_1)d_1(y_{\tau_1}-v_2)-(c_1+\delta_1)(x-v_1)-d_1(y-v_2)\\ \dot{y}(t) &= 2(1-a_2)d_2(x_{\tau_2}-v_1)+2(1-a_2)c_2(y_{\tau_2}-v_2)-d_2(x-v_1)-(c_2+\delta_2)(y-v_2),\end{aligned} \tag{4.5}$$

where

$$c_1 = \alpha_1(v_1,v_2)+v_1\frac{\partial\alpha_1(v_1,v_2)}{\partial x}, \quad d_1 = v_1\frac{\partial\alpha_1(v_1,v_2)}{\partial y}$$
$$c_2 = \alpha_2(v_1,v_2)+v_2\frac{\partial\alpha_2(v_1,v_2)}{\partial y}, \quad d_2 = v_2\frac{\partial\alpha_2(v_1,v_2)}{\partial x}.$$

The analysis for the steady state with $x > 0$ and $y = 0$

For the examination of the stability of E_1, we start by looking at the steady state by writing

$$x = \bar{x} + Ae^{\lambda t}$$

and

$$y = 0 + Be^{\lambda t}.$$

By evaluating c_1, c_2, d_1, d_2 at E_1, we obtain

$$\begin{aligned}\lambda Ae^{\lambda t} &= 2(1-a_1)c_1e^{-\lambda\tau_1}Ae^{\lambda t}+2(1-a_1)d_1e^{-\lambda\tau_1}Be^{\lambda t}-(c_1+\delta_1)Ae^{\lambda t}-d_1Be^{\lambda t}\\ \lambda Be^{\lambda t} &= 2(1-a_2)c_2e^{-\lambda\tau_2}Be^{\lambda t}-(c_2+\delta_2)Be^{\lambda t}.\end{aligned}$$

We put this system in matrix form and write

$$\begin{pmatrix}\lambda Ae^{\lambda t}\\ \lambda Be^{\lambda t}\end{pmatrix} = \begin{pmatrix}2(1-a_1)c_1e^{-\lambda\tau_1}-(c_1+\delta_1) & 2(1-a_1)d_1e^{-\lambda\tau_1}-d_1\\ 0 & 2(1-a_2)c_2e^{-\lambda\tau_2}-(c_2+\delta_2)\end{pmatrix}\begin{pmatrix}Ae^{\lambda t}\\ Be^{\lambda t}\end{pmatrix}$$

For stability to exist, the real part of all of the eigenvalues must be less than or equal to zero. To solve for the eigenvalues of the variational matrix, we must solve for the roots of the characteristic polynomial from the above

$$D(\lambda) = [\lambda + (c_1 + \delta_1) - 2(1 - a_1)c_1 e^{-\lambda\tau_1}][\lambda + (c_2 + \delta_2) - 2(1 - a_2)c_2 e^{-\lambda\tau_2}] = 0.$$

Therefore, we have either

$$\lambda + (c_1 + \delta_1) - 2(1 - a_1)c_1 e^{-\lambda\tau_1} = 0,$$

or

$$\lambda + (c_2 + \delta_2) - 2(1 - a_2)c_2 e^{-\lambda\tau_2} = 0.$$

Set $Q(\lambda) = \lambda + (c_2 + \delta_2) - 2(1 - a_2)c_2 e^{-\lambda\tau_2}$, which determines the stability of the steady state $y = 0$. Then

$$\begin{aligned} R &=: Re(Q(i\omega)) = (c_2 + \delta_2) - 2(1 - a_2)c_2 \cos(\omega\tau_2) \\ I &=: Im(Q(i\omega)) = \omega + 2(1 - a_2)c_2 \sin(\omega\tau_2). \end{aligned}$$

Let $\phi(\omega)$ denote an argument of the vector $Q(i\omega)$. Then we have

$$\cos(\phi(\omega)) = \frac{R}{(R^2 + I^2)^{1/2}},$$

$$\sin(\phi(\omega)) = \frac{I}{(R)^2 + I^2)^{1/2}}.$$

After substitution, one obtains

$$\cos(\phi(\omega)) = \frac{o(\omega)}{(\omega^2 + o(\omega^2))^{1/2}} \longrightarrow 0 \; as \; \omega \to +\infty,$$

$$\sin(\phi(\omega)) = \frac{\omega + o(\omega)}{(\omega^2 + o(\omega^2))^{1/2}} \longrightarrow 1 \; as \; \omega \to +\infty.$$

Thus ϕ converges to $\phi_k = \frac{\pi}{2} + 2k\pi$ as $\omega \to +\infty$, where k is an integer. The initial angle is either equal to $\phi_p = \pi$ if $c_2 + \delta_2 < 2(1 - a_2)c_2$ or to $\phi_p = 0$ if $c_2 + \delta_2 > 2(1 - a_2)c_2$. Let

us see when the increment of ϕ is equal to $\frac{\pi}{2}$.

Case 1. $c_2 + \delta_2 < 2(1 - a_2)c_2$.

In this case, Q is unstable when $\tau_2 = 0$; when $\tau_2 \neq 0$, we have

$$\Delta(\phi) = \phi_k - \phi_p = -\frac{\pi}{2} + 2k\pi,$$

$$-\frac{\pi}{2} + 2k\pi = \frac{\pi}{2},$$

$$k = \frac{1}{2},$$

which contradicts the assumption that k is an integer. It follows from *Mikhailov's theorem* that there exists at least one eigenvalue with positive real part and E_1 is unstable, independent of τ_2.

Case 2. $c_2 + \delta_2 > 2(1 - a_2)c_2$ and $|c_2 + \delta_2| > |2(1 - a_2)c_2|$.

In this situation, Q is stable when $\tau_2 = 0$; when $\tau_2 \neq 0$, we obtain

$$\Delta(\phi) = \phi_k - \phi_p = \frac{\pi}{2} + 2k\pi,$$

$$\frac{\pi}{2} + 2k\pi = \frac{\pi}{2},$$

$$k = 0.$$

Note that we have either $c_2 + \delta_2 > 2(1 - a_2)c_2 > 0$ or $c_2 + \delta_2 > 0$ and $2(1 - a_2)c_2 < 0$ in this case, which shows that $Q(i\omega)$ stays in the right-hand complex half-plane(because $Re(Q(i\omega)) > 0$). Therefore, stability does not depend on τ_2.

Case 3. $c_2 + \delta_2 > 2(1 - a_2)c_2$ and $|c_2 + \delta_2| < |2(1 - a_2)c_2|$.

Under this situation, Q is still stable when $\tau_2 = 0$; but if $\tau_2 < -\frac{1}{2(1-a_2)c_2}$, then $Im(Q(i\omega))$ increases as ω increases from 0 to $+\infty$. $Re(Q(i\omega))$ oscillates between $c_2+\delta_2-2(1-a_2)c_2$ and $c_2+\delta_2+2(1-a_2)c_2$. It is clear from the above that $arg(Q(i\omega)) \to \frac{\pi}{2}$ as $\omega \to +\infty$ and $arg(Q(0)) = 0$. Therefore, $\Delta = \frac{\pi}{2}$. When τ_2 increases, $Im(Q(i\omega))$ starts to oscillate and $Q(i\omega)$ may intersect the real axis. We suppose that the point of intersection is $\bar{\omega}$ such that $Re(Q(i\omega)) = 0$. This implies that $\cos(\bar{\omega}\bar{\tau}_2)=\frac{c_2+\delta_2}{2(1-a_2)c_2}$. The

change of stability occurs for such values of $\bar{\omega}$ and $\bar{\tau}_2$ that $Im(Q(i\bar{\omega})) = 0$. Therefore, $\bar{\omega} = \{(2(1-a_2)c_2)^2 - (c_2+\delta_2)^2\}^{1/2}$ and $\bar{\tau}_2 = \frac{1}{\bar{\omega}} \arccos(\frac{c_2+\delta_2}{2(1-a_2)c_2})$.

As a result, we have the following lemma.

Lemma 4.3.1 *For system (4.4), the steady state $y = 0$ is stable (independent of τ_2) if $c_2+\delta_2 > 2(1-a_2)c_2$ and $c_2+\delta_2+2(1-a_2)c_2 > 0$. In the case that $c_2+\delta_2 < 2(1-a_2)c_2$, there exists at least one eigenvalue with positive real part and $y = 0$ is unstable. However, if $c_2+\delta_2 > 2(1-a_2)c_2$ and $c_2+\delta_2+2(1-a_2)c_2 < 0$, then there is a threshold value of the delay, $\bar{\tau}_2$ such that for $\tau_2 < \bar{\tau}_2$, the steady state $y = 0$ is stable and for $\tau_2 > \bar{\tau}_2$, is unstable.*

Alternatively, we consider the stability of the steady state $x = \bar{x}$ which is determined by the characteristic equation

$$\lambda + (c_1+\delta_1) - 2(1-a_1)c_1 e^{-\lambda\tau_1} = 0.$$

Following the same steps as before, we have the following lemma.

Lemma 4.3.2 *For system (4.4), the steady state $x = \bar{x}$ is stable (independent of τ_1) if $c_1+\delta_1 > 2(1-a_1)c_1$ and $c_1+\delta_1+2(1-a_1)c_1 > 0$. In the case that $c_1+\delta_1 < 2(1-a_1)c_1$, there exists at least one eigenvalue with positive real part and $x = \bar{x}$ is unstable. However, if $c_1+\delta_1 > 2(1-a_1)c_1$ and $c_1+\delta_1+2(1-a_1)c_1 < 0$, then there is a threshold value of the delay, $\bar{\tau}_1$ such that for $\tau_1 < \bar{\tau}_1$, the steady state $x = \bar{x}$ is stable and for $\tau_1 > \bar{\tau}_1$, is unstable.*

Based on *Lemma* 4.3.1 and 4.3.2, we obtain the following theorem.

Theorem 4.3.2 *For system (4.4), the steady state E_1 is stable for all $\tau_i \geq 0$ if $c_i+\delta_i > 2(1-a_i)c_i$ and $c_i+\delta_i+2(1-a_i)c_i > 0$. In the case that $c_1+\delta_1 < 2(1-a_1)c_1$, or $c_2+\delta_2 < 2(1-a_2)c_2$ there exists at least one eigenvalue with positive real part and E_1 is unstable. However, if $c_i+\delta_i > 2(1-a_i)c_i$ and $c_i+\delta_i+2(1-a_i)c_i < 0$, then there is a threshold value of the delay, $\bar{\tau}_i$ such that for $\tau_i < \bar{\tau}_i$, the steady state E_1 is stable and for $\tau_1 > \bar{\tau}_1$, or $\tau_2 > \bar{\tau}_2$ is unstable. Here $i = 1, 2$.*

The analysis for the steady state with $x = 0$ and $y > 0$

Now we will examine the steady state $E_2(0, \bar{y})$. We write

$$x(t) = 0 + Ce^{\lambda t}$$

and

$$y(t) = \bar{y} + De^{\lambda t}.$$

Following exactly as we did for the previous steady state, we find

$$\begin{pmatrix} \lambda Ce^{\lambda t} \\ \lambda De^{\lambda t} \end{pmatrix} = \begin{pmatrix} 2(1-a_1)c_1e^{-\lambda\tau_1} - (c_1+\delta_1) & 0 \\ 2(1-a_2)c_2e^{-\lambda\tau_2} - d_2 & 2(1-a_2)c_2e^{-\lambda\tau_2} - (c_2+\delta_2) \end{pmatrix} \begin{pmatrix} Ce^{\lambda t} \\ De^{\lambda t} \end{pmatrix},$$

where we have evaluated the derivatives c_1, c_2, d_1, d_2 at the point $(0, \bar{y})$ instead of at $(\bar{x}, 0)$. The stability of the steady state $E_2(0, \bar{y})$ is determined by the characteristic equation

$$[\lambda + (c_1 + \delta_1) - 2(1-a_1)c_1e^{-\lambda\tau_1}][\lambda + (c_2 + \delta_2) - 2(1-a_2)c_2e^{-\lambda\tau_2}] = 0.$$

Similarly, we examine different cases for the characteristic equations and obtain the following theorem.

Theorem 4.3.3 *For system (4.4), the steady state E_2 is stable for all $\tau_i \geq 0$ provided that $c_i + \delta_i > 2(1-a_i)c_i$ and $c_i + \delta_i + 2(1-a_i)c_i > 0$. When either $c_1 + \delta_1 < 2(1-a_1)c_1$, or $c_2 + \delta_2 < 2(1-a_2)c_2$ there exists at least one eigenvalue with positive real part and E_2 is unstable. However, in the case that $c_i + \delta_i > 2(1-a_i)c_i$ and $c_i + \delta_i + 2(1-a_i)c_i < 0$, there is a threshold value of the delay, $\bar{\tau}_i$ such that for $\tau_i < \bar{\tau}_i$, the steady state E_2 is stable and for $\tau_1 > \bar{\tau}_1$, or $\tau_2 > \bar{\tau}_2$ is unstable. Here $i = 1, 2$.*

The analysis for the steady state with $x > 0$ and $y > 0$

In order to examine the stability of interior equilibria, we employ the theorem in [99] stated below.

Theorem 4.3.4 *Consider the n-dimensional linear autonomous retarded functional differential equation(RFDE)*

$$\dot{x}(t) = \int_{-\infty}^{0} [d\eta(\theta)]x(t+\theta)$$

and suppose that there exists a scalar $\nu > 0$ such that

$$\int_{-\infty}^{0} e^{-\nu\theta}|d\eta_{jk}(\theta)| < +\infty, \ j,k = 1,...,n,$$

where $\eta(\theta)$ is an $n \times n$ matrix function on $[-\infty, 0]$ of bounded variation.

The characteristic function assumes the form

$$D(\lambda) = det(\lambda I - \int_{-\infty}^{0} e^{\lambda\theta} d\eta(\theta)).$$

Let $\rho_1 \geq ... \geq \rho_r \geq 0$ and $\sigma_1 \geq ... \geq \sigma_s \geq 0$ denote the non-negative real zeros of R and S respectively, where

$$R(\omega) = ReD(i\omega), \ \ S(\omega) = ImD(i\omega).$$

The trivial solution $x = 0$ of the RFDE is exponentially asymptotically stable if and only if

$$n = 2m,$$

$$S(\rho_k) \neq 0, \ k = 1,...,r,$$

$$\sum_{k=1}^{r}(-1)^k sgnS(\rho_k) = (-1)^m m;$$

or

$$n = 2m + 1,$$

$$R(\sigma_k) \neq 0, \ k = 1,...,s-1,$$

$$R(0) > 0,$$

$$\sum_{k=1}^{s-1} sgnR(\sigma_k) + \frac{1}{2}((-1)^s + (-1)^m) + (-1)^m m = 0.$$

We will proceed as we did for the other steady states and write

$$x(t) = x^* + Be^{\lambda t}$$

and

$$y(t) = y^* + Ce^{\lambda t}.$$

Substituting into (4.5) and evaluating $c_i, d_i, i = 1, 2$ at (x^*, y^*), we obtain

$$\lambda Be^{\lambda t} = [2(1-a_1)c_1e^{-\lambda\tau_1} - (c_1+\delta_1)]Be^{\lambda t} + [2(1-a_1)d_1e^{-\lambda\tau_1} - d_1]Ce^{\lambda t}$$

and

$$\lambda Ce^{\lambda t} = [2(1-a_2)d_2e^{-\lambda\tau_2} - d_2]Be^{\lambda t} + [2(1-a_2)c_2e^{-\lambda\tau_2} - (c_2+\delta_2)]Ce^{\lambda t}.$$

We put this system in matrix form and write

$$\begin{pmatrix} \lambda Be^{\lambda t} \\ \lambda Ce^{\lambda t} \end{pmatrix} = \begin{pmatrix} 2(1-a_1)c_1e^{-\lambda\tau_1} - (c_1+\delta_1) & 2(1-a_1)d_1e^{-\lambda\tau_1} - d_1 \\ 2(1-a_2)d_2e^{-\lambda\tau_2} - d_2 & 2(1-a_2)c_2e^{-\lambda\tau_2} - (c_2+\delta_2) \end{pmatrix} \begin{pmatrix} Be^{\lambda t} \\ Ce^{\lambda t} \end{pmatrix} \tag{4.6}$$

For stability to exist, the real part of all of the eigenvalues must be less than or equal to zero. To solve for the eigenvalues of the variational matrix, we must solve for the roots of the characteristic polynomial from (4.6)

$$D(\lambda) = \lambda^2 + m_1\lambda + m_0 + (p_1\lambda + p_0)e^{-\lambda\tau_2} + (q_1\lambda + q_0)e^{-\lambda\tau_1} + \gamma_0 e^{-\lambda(\tau_1+\tau_2)} \tag{4.7}$$

where

$$m_1 = c_1 + c_2 + \delta_1 + \delta_2, \quad p_1 = -2(1-a_2)c_2, \quad q_1 = -2(1-a_1)c_1,$$

$$p_0 = 2(1-a_1)d_1d_2 - 2(1-a_2)c_2(c_1+\delta_1), \qquad m_0 = (c_1+\delta_1)(c_2+\delta_2) - d_1d_2,$$

$$q_0 = 2(1-a_2)d_1d_2 - 2(1-a_1)c_1(c_2+\delta_2), \ \gamma_0 = 4(1-a_1)(1-a_2)(c_1c_2 - d_1d_2).$$

Thus

$$\begin{aligned} R(\omega) &= -\omega^2 + m_0 + p_1\omega\sin(\tau_2\omega) + q_1\omega\sin(\tau_1\omega) \\ &+ p_0\cos(\tau_2\omega) + q_0\cos(\tau_1\omega) + \gamma_0\cos((\tau_1+\tau_2)\omega), \end{aligned}$$

$$\begin{aligned} S(\omega) &= m_1\omega + p_1\omega\cos(\tau_2\omega) + q_1\omega\cos(\tau_1\omega) \\ &- p_0\sin(\tau_2\omega) - q_0\sin(\tau_1\omega) - \gamma_0\sin((\tau_1+\tau_2)\omega). \end{aligned}$$

For $\omega \in (0, +\infty)$, the following inequalities hold:

$$|\cos(\tau\omega)| \leq 1, \ -\sin((\tau_1+\tau_2)\omega) > -(\tau_1+\tau_2)\omega$$

and

$$\sin(\tau\omega) > -0.22\tau\omega\,.$$

With the help of them, S can be estimated in the following ways:

$$S(\omega) \geq S^{-}(\omega) = (m_1 - |p_1| - |q_1| - 0.22|p_0|\tau_1 - 0.22|q_0|\tau_1) - |\gamma_0|(\tau_1 + \tau_2))\omega.$$

Thus, it follows that if

$$(|\gamma_0| + 0.22|p_0|)\tau_1 + (|\gamma_0| + 0.22|q_0|)\tau_2 < m_1 - |p_1| - |q_1|,$$

then

$$S(\omega) \geq S^{-}(\omega) > 0,\ \omega \in (0, +\infty).$$

On the other hand, since $\lim_{\omega \to +\infty} R(\omega) = -\infty$, the number r of the positive zeros ρ_k of R is odd if $R(0) = m_0 + p_0 + q_0 + \gamma_0 > 0$. Hence we have

$$\sum_{k=1}^{r}(-1)^k sgnS(\rho_k) = -1\,.$$

This means that the stability conditions in *Theorem* 4.3.3 are satisfied.

As a result, we have the following theorem.

Theorem 4.3.5 *For system (4.4), the interior equilibrium E_3 is exponentially asymptotically stable if*

$$m_0 + p_0 + q_0 + \gamma_0 > 0$$

$$(|\gamma_0| + 0.22|q_0|)\tau_1 + (|\gamma_0| + 0.22|p_0|)\tau_2 < (2a_1 - 1)c_1 + \delta_1 + (2a_2 - 1)c_2 + \delta_2\,.$$

Corollary 4.3.6 *For system (4.4), the interior equilibrium is unstable if*

$$m_0 + p_0 + q_0 + \gamma_0 \leq 0\,.$$

Proof. If $m_0 + p_0 + q_0 + \gamma_0 = 0$ then $D(0) = 0$, zero is a root of the characteristic equation and D is not stable,i.e. the interior equilibrium E_3 is unstable. If $m_0 + p_0 + q_0 + \gamma_0 < 0$ then there exists at least one positive real root of the characteristic equation since

$$\lim_{h \to +\infty} D(h) = +\infty,\ h \in \Re$$

and D is continuous in $[0, +\infty)$. In this case D is not stable either. □

4.4 The continuous treatment case

Here we consider the case where chemotherapy is applied continuously. In this case the model becomes (4.1) and we rewrite it here as

$$\begin{aligned}
\dot{x}(t) &= 2(1-a_1)x_{\tau_1}\alpha_1(x_{\tau_1},y_{\tau_1}) - x\alpha_1(x,y) - \delta_1 x(t) - p_1(x)w(u) \\
\dot{y}(t) &= 2(1-a_2)y_{\tau_2}\alpha_2(x_{\tau_2},y_{\tau_2}) - y\alpha_2(x,y) - \delta_2 y(t) - p_2(y)w(u) \\
\dot{u}(t) &= \delta - [\gamma + \eta_1 p_1(x) + \eta_2 p_2(y)]w(u).
\end{aligned}$$

The equilibria for system (4.1) are $F_0(0,0,u_0)$, $F_1(\hat{x},0,\hat{u}_1)$, $F_2(0,\hat{y},\hat{u}_2)$, and $F_3(\tilde{x},\tilde{y},\tilde{u})$, where u_0 is the positive solution of $w(u) = \gamma^{-1}\delta$, providing it exists.

In order for F_1 to exist, the algebraic system

$$\begin{aligned}
(1-2a_1)x\alpha_1(x,0) - \delta_1 x - p_1(x)w(u) = 0 \\
\delta - [\gamma + \eta_1 p_1(x)]w(u) = 0
\end{aligned} \tag{4.8}$$

must have a positive solution. It follows from (4.8) that

$$(1-2a_1)x\alpha_1(x,0) - \delta_1 x = \frac{\delta p_1(x)}{\gamma + \eta_1 p_1(x)}.$$

We write this as $\varphi(x) = \psi(x)$.

Since $x = \bar{x}$ is an equilibrium in the no treatment case, $\varphi(\bar{x}) = (1-2a_1)\bar{x}\alpha_1(\bar{x},0) - \delta_1\bar{x} = 0$ and $\varphi(0) = 0$, $\varphi'(K_1) = -\delta_1 < 0$, $\varphi(x) > 0, 0 < x < \bar{x}$. Since $\psi(0) = 0$, $\psi(x) > 0$, $\psi'(x) > 0, x > 0$, there will be a positive intersection of the curves $z = \varphi(x)$ and $z = \psi(x)$ provided $\psi'(0) < \varphi'(0)$. But $\psi'(0) = \delta\gamma^{-1}p_1{}'(0)$ and $\varphi'(0) = (1-2a_1)\alpha_1(0,0) - \delta_1$. Hence we assume that

$$\delta p_1{}'(0) + \delta_1\gamma < \gamma(1-2a_1)\alpha_1(0,0), \tag{4.9}$$

which guarantees that F_1 exists uniquely. Note that (4.9) also guarantees the existence of E_1.

Similarly, F_2 exists if

$$\delta p_2{}'(0) + \delta_2\gamma < \gamma(1-2a_2)\alpha_2(0,0).$$

Note that from a biological standpoint, neither F_0 nor F_2 can occur, since in either case, there are no healthy cells left(presumably death has occurred).

Before discussing the existence question for F_3, the interior equilibrium, we analyze the stability of the boundary equilibria. We first linearize system (4.1) about a general point (v_1, v_2, v_3) and obtain the variational matrix M of the form

$$M = \begin{pmatrix} 2(1-a_1)c_1e^{-\lambda\tau_1} - (c_1+\delta_1+\xi_1) & 2(1-a_1)d_1e^{-\lambda\tau_1} - d_1 & -\mu_1 \\ 2(1-a_2)d_2e^{-\lambda\tau_2} - d_2 & 2(1-a_2)c_2e^{-\lambda\tau_2} - (c_2+\delta_2+\xi_2) & -\mu_2 \\ -\xi_1\eta_1 & -\xi_2\eta_2 & -\bar{\gamma} \end{pmatrix} \tag{4.10}$$

where $\xi_i = p_i'(v_i)w(v_3)$, $\mu_i = p_i(v_i)w'(v_3)$, $\bar{\gamma} = [\gamma + \eta_1 p_1(v_1) + \eta_2 p_2(v_2)]w'(v_3)$ and c_i, d_i are evaluated at the point (v_1, v_2, v_3).

Evaluating the variational matrices M about F_1, we get that

$$M_1 = \begin{pmatrix} 2(1-a_1)c_1e^{-\lambda\tau_1} - (c_1+\delta_1+\xi_1) & 2(1-a_1)d_1e^{-\lambda\tau_1} - d_1 & -\mu_1 \\ 0 & 2(1-a_2)c_2e^{-\lambda\tau_2} - (c_2+\delta_2+\xi_2) & 0 \\ -\xi_1\eta_1 & -\xi_2\eta_2 & -\bar{\gamma} \end{pmatrix}.$$

Hence the eigenvalues satisfy

$$[\lambda + c_2 + \delta_2 + \xi_2 - 2(1-a_2)c_2e^{-\lambda\tau_2}][\lambda^2 + \rho_1\lambda + \rho_0 - (q_1\lambda + q_0)e^{-\lambda\tau_1}] = 0,$$

where

$$\rho_1 = c_1+\delta_1+\xi_1+\bar{\gamma},\ \rho_0 = (c_1+\delta_1+\xi_1)\bar{\gamma} - \mu_1\xi_1\eta_1,\ q_1 = 2(1-a_1)c_1,\ q_0 = 2(1-a_1)c_1\bar{\gamma}.$$

Note that $Q_1(\lambda) = \lambda + c_2 + \delta_2 + \xi_2 - 2(1-a_2)c_2e^{-\lambda\tau_2} = 0$ determines the stability of the steady sate $y = 0$; while $Q_2(\lambda) = \lambda^2 + \rho_1\lambda + \rho_0 - (q_1\lambda + q_0)e^{-\lambda\tau_1} = 0$ determines the stability of both $x = \hat{x}$ and $u = \hat{u}_1$. The following lemmas are special cases in [64] and proved by Liu and Freedman [64].

Lemma 4.4.1 *For system (4.1), the steady state $y = 0$ is stable for all $\tau_2 \geq 0$ if $2(1-a_2)c_2 < c_2 + \delta_2 + \xi_2$ and $2(1-a_2)c_2 + c_2 + \delta_2 + \xi_2 > 0$. Assume that $2(1-a_2)c_2 >$*

$c_2+\delta_2+\xi_2$. Then there exists at least one eigenvalue with positive real part and $y=0$ becomes unstable. However, if $2(1-a_2)c_2 < c_2+\delta_2+\xi_2$ and $2(1-a_2)c_2+c_2+\delta_2+\xi_2<0$, then there is a threshold value $\bar{\tau}_2 = \arccos(\frac{c_2+\delta_2+\xi_2}{2(1-a_2)c_2})/[(2(1-a_2)c_2)^2-(c_2+\delta_2+\xi_2)^2]^{\frac{1}{2}}$, such that for $\tau_2<\bar{\tau}_2$, $y=0$ is stable and for $\tau_2>\bar{\tau}_2$, is unstable.

Lemma 4.4.2 *For system (4.1), suppose that $({\rho_1}^2-2\rho_0-{q_1}^2)^2 < 4({\rho_0}^2-{q_0}^2)$. Then if $q_1<\rho_1$ and $(\rho_1-q_1)^2 \le 4(\rho_0-q_0)$, both the steady states $\hat{x}$ and $u=\hat{u}_1$ are stable for all $\tau_1 \ge 0$; whereas if $q_1>\rho_1$, $x=\hat{x}$ and $u=\hat{u}_1$ become unstable for all $\tau_1 \ge 0$. Assume that $({\rho_1}^2-2\rho_0-{q_1}^2)^2 \ge 4({\rho_0}^2-{q_0}^2)$ and ${q_1}^2+2\rho_0-{\rho_1}^2>0$. Then as τ_1 increases, stability switches may occur. There exists a positive $\bar{\tau}_1$ such that $Q_2(\lambda)$ is unstable for all $\tau_1>\bar{\tau}_1$. As τ_1 varies from 0 to $\bar{\tau}_1$, at most a finite number of stability switches may occur and $Q_2(\lambda)$ bifurcates at $\tau_1=\bar{\tau}_1$.*

Based on *Lemma* 4.4.1 and 4.4.2, we have the following theorems.

Theorem 4.4.1 *For system (4.1), assume that $({\rho_1}^2-2\rho_0-{q_1}^2)^2 < 4({\rho_0}^2-{q_0}^2)$. Then*

1) the steady state F_1 is stable for all $\tau_i \ge 0$ provided that $q_1<\rho_1$ and $(\rho_1-q_1)^2 \le 4(\rho_0-q_0)$, $2(1-a_2)c_2 < c_2+\delta_2+\xi_2$ and $2(1-a_2)c_2+c_2+\delta_2+\xi_2>0$;

2) the steady state F_1 becomes unstable if either $q_1>\rho_1$, or $2(1-a_2)c_2 > c_2+\delta_2+\xi_2$.

Theorem 4.4.2 *For system (4.1), suppose that $({\rho_1}^2-2\rho_0-{q_1}^2)^2 \ge 4({\rho_0}^2-{q_0}^2)$, ${q_1}^2+2\rho_0>{\rho_1}^2$, $2(1-a_2)c_2<c_2+\delta_2+\xi_2$ and $2(1-a_2)c_2+c_2+\delta_2+\xi_2<0$. Then as τ_i increases, stability switches may occur. There exists $\bar{\tau}_i>0$ such that the steady state F_1 is stable for $\tau_i<\bar{\tau}_i$ and unstable for $\tau_i>\bar{\tau}_i$. Further F_1 bifurcates at $\tau_i=\bar{\tau}_i, i=1,2$.*

Evaluating the variational matrix M about F_2, we obtain that

$$M_2=\begin{pmatrix} 2(1-a_1)c_1e^{-\lambda\tau_1}-(c_1+\delta_1+\xi_1) & 0 & 0 \\ 2(1-a_2)d_2e^{-\lambda\tau_2}-d_2 & 2(1-a_2)c_2e^{-\lambda\tau_2}-(c_2+\delta_2+\xi_2) & -\mu_2 \\ -\xi_1\eta_1 & -\xi_2\eta_2 & -\bar{\gamma} \end{pmatrix}.$$

Hence the eigenvalues satisfy

$$[\lambda+c_1+\delta_1+\xi_1-2(1-a_1)c_1e^{-\lambda\tau_1}][\lambda^2+l_1\lambda+l_0-(m_1\lambda+m_0)e^{-\lambda\tau_2}]=0,$$

where

$$l_1=c_2+\delta_2+\xi_2+\bar{\gamma},\ l_0=(c_2+\delta_2+\xi_2)\bar{\gamma}-\mu_2\xi_2\eta_2,\ m_1=2(1-a_2)c_2,\ m_0=2(1-a_2)c_2\bar{\gamma}.$$

By using the same methods as we did before, we obtain:

Theorem 4.4.3 *For system (4.1), assume that* $({l_1}^2 - 2l_0 - {m_1}^2)^2 < 4({l_0}^2 - {m_0}^2)$. *Then*

1) the steady state F_2 *is stable for all* $\tau_i \geq 0$ *provided that* $m_1 < l_1$ *and* $(l_1 - m_1)^2 \leq 4(l_0 - m_0)$, $2(1-a_1)c_1 < c_1 + \delta_1 + \xi_1$ *and* $2(1-a_1)c_1 + c_1 + \delta_1 + \xi_1 > 0$;

2) the steady state F_2 *becomes unstable if either* $m_1 > l_1$ *or* $2(1-a_1)c_1 > c_1 + \delta_1 + \xi_1$.

Theorem 4.4.4 *For system (4.1), suppose that* $({l_1}^2 - 2l_0 - {m_1}^2)^2 \geq 4({l_0}^2 - {m_0}^2)$, ${m_1}^2 + 2l_0 > {l_1}^2$, $2(1-a_1)c_1 < c_1 + \delta_1 + \xi_1$ *and* $2(1-a_1)c_1 + c_1 + \delta_1 + \xi_1 < 0$. *Then as* τ_i *increases, stability switches may occur. There exists* $\bar{\tau}_i > 0$ *such that the steady state* F_2 *is stable for* $\tau_i < \bar{\tau}_i$ *and unstable for* $\tau_i > \bar{\tau}_i$. *Further* F_2 *bifurcates at* $\tau_i = \bar{\tau}_i, i = 1, 2$. *Here* $\bar{\tau}_1 = \arccos(\frac{c_1+\delta_1+\xi_1}{2(1-a_1)c_1})/[(2(1-a_1)c_1)^2 - (c_1+\delta_1+\xi_1)^2]^{\frac{1}{2}}$.

Evaluating the variational matrix M about F_3, we obtain that

$$M_3 = \begin{pmatrix} 2(1-a_1)c_1e^{-\lambda\tau_1} - (c_1+\delta_1+\xi_1) & 2(1-a_1)d_1e^{-\lambda\tau_1} - d_1 & -\mu_1 \\ 2(1-a_2)d_2e^{-\lambda\tau_2} - d_2 & 2(1-a_2)c_2e^{-\lambda\tau_2} - (c_2+\delta_2+\xi_2) & -\mu_2 \\ -\xi_1\eta_1 & -\xi_2\eta_2 & -\bar{\gamma} \end{pmatrix}.$$

Therefore, the eigenvalues satisfy

$$e^{-\lambda(\tau_1+\tau_2)}H(\lambda) = 0,$$

where

$$H(\lambda) = \lambda^3 e^{\lambda(\tau_1+\tau_2)} + \lambda^2(A_2e^{\lambda(\tau_1+\tau_2)} + B_2e^{\lambda\tau_2} + C_2e^{\lambda\tau_1}) + \lambda(A_1e^{\lambda(\tau_1+\tau_2)} + B_1e^{\lambda\tau_2} + C_1e^{\lambda\tau_1} + D_1) + A_0e^{\lambda(\tau_1+\tau_2)} + B_0e^{\lambda\tau_2} + C_0e^{\lambda\tau_1} + D_0$$

$$\begin{aligned}
D_1 &= 4(1-a_1)(1-a_2)c_1c_2 - 4(1-a_1)(1-a_2)d_1d_2 \\
C_1 &= d_2D_1 - 2(1-a_2)c_2\bar{\gamma} - 2(c_1+\delta_1+\xi_1)(1-a_2)c_2 \\
B_1 &= d_1D_2 - 2(1-a_1)c_1\bar{\gamma} - 2(c_2+\delta_2+\xi_2)(1-a_1)c_1 \\
A_2 &= c_1+\delta_1+\xi_1+c_2+\delta_2+\xi_2+\bar{\gamma}, \quad B_2 = -2(1-a_1)c_1, \quad C_2 = -2(1-a_2)c_2 \\
A_1 &= (c_1+\delta_1+\xi_1+c_2+\delta_2+\xi_2)\bar{\gamma} + (c_1+\delta_1+\xi_1)(c_2+\delta_2+\xi_2) - d_1d_2 - \mu_1\xi_1\eta_1 - \mu_2\xi_2\eta_2; \\
D_0 &= 4(1-a_1)(1-a_2)(c_1c_2 - d_1d_2)\bar{\gamma} \\
C_0 &= 2(1-a_1)d_1(\mu_2\xi_1\eta_1 + d_2\bar{\gamma}) - 2(1-a_2)c_2(\mu_1\xi_1\eta_1 + (c_1+\delta_1+\xi_1)\bar{\gamma}) \\
B_0 &= 2(1-a_2)d_2(\mu_1\xi_2\eta_2 + d_1\bar{\gamma}) - 2(1-a_1)c_1(\mu_2\xi_2\eta_2 + (c_2+\delta_2+\xi_2)\bar{\gamma}) \\
A_0 &= \mu_1\xi_2\eta_2d_2 + \mu_2\xi_1\eta_1d_1 - \mu_1\xi_1\eta_1(c_2+\delta_2+\xi_2) - \mu_2\xi_2\eta_2(c_1+\delta_1+\xi_1).
\end{aligned}$$

Theorem 4.4.5 *For system (4.1), suppose that $A_0 + B_0 + C_0 + D_0 \neq 0$. Then a necessary and sufficient condition for all the zeros of $H(\lambda)$ to have negative real parts is that*

(a) in the interval $[-2k_1\pi/(\tau_1+\tau_2), 2k_1\pi/(\tau_1+\tau_2)]$, the function $G(y) = Im(H(iy))$, $y \in R, i = \sqrt{-1}$, has exactly $4k_1 + 3$ zeros, and

(b) the condition $F(y_0)G'(y_0) > 0$, where $F(y) = Re(H(iy))$, is satisfied for the zeros y_0 in the interval $[-2k_1\pi/(\tau_1+\tau_2), k_1\pi/(\tau_1+\tau_2)]$, where k_1 is equal to $max(k_0, k_0')$, where k_0 and k_0' are the smallest integers for which

$$B_k > \sqrt{2}A_k,\ k \geq k_0; \quad B_k > \sqrt{2}A_k',\ k \geq k_0'$$

with

$$A_k = \frac{4(k+1)^2\pi^2}{(\tau_1+\tau_2)^2}(|A_2|+|B_2|+|C_2|)+\frac{2(k+1)\pi}{\tau_1+\tau_2}(|A_1|+|B_1|+|C_1|+|D_1|)+(|A_0|+|B_0|+|C_0|)$$

$$\begin{aligned} A_k' = \frac{4(k'+1)^2\pi^2}{(\tau_1+\tau_2)^3}(3+(\tau_1+\tau_2)|A_2|+\tau_2|B_2|+\tau_1|C_2|) + \frac{2(k'+1)\pi}{(\tau_1+\tau_2)^2}(2(|A_2|+|B_2|+|C_2|) \\ +(\tau_1+\tau_2)|A_1|+\tau_2|B_1|+\tau_1|C_1|) + \frac{1}{\tau_1+\tau_2}(|A_1|+|B_1|+|C_1| \\ +(\tau_1+\tau_2)|A_0|+\tau_2|B_0|+\tau_1|C_0|+|D_0|) \end{aligned}$$

and

$$B_k = k^2\pi^2/\tau^2.$$

Further, if $A_0 + B_0 + C_0 + D_0 = 0$, then $H(\lambda)$ is unstable.

Proof. For our polynomial, the functions $F(y)$ and $G(y)$ take the form

$$\begin{aligned} F(y) = y^3\sin[(\tau_1+\tau_2)y] - y^2\{A_2\cos[(\tau_1+\tau_2)y] + B_2\cos(\tau_2 y) + C_2\cos(\tau_1 y)\} \\ -y\{A_1\sin[(\tau_1+\tau_2)y] + B_1\sin(\tau_2 y) + C_1\sin(\tau_1 y)\} \\ +A_0\cos[(\tau_1+\tau_2)y] + B_0\cos(\tau_2 y) + C_0\cos(\tau_1 y) + D_0, \end{aligned}$$

$$\begin{aligned} G(y) = y^3\cos[(\tau_1+\tau_2)y] - y^2\{A_2\sin[(\tau_1+\tau_2)y] + B_2\sin(\tau_2 y) + C_2\sin(\tau_1 y)\} \\ +y\{A_1\cos[(\tau_1+\tau_2)y] + B_1\cos(\tau_2 y) + C_1\cos(\tau_1 y) + D_1\} \\ +A_0\sin[(\tau_1+\tau_2)y] + B_0\sin(\tau_2 y) + C_0\sin(\tau_1 y). \end{aligned}$$

We will also need $G'(y)$.

$$G'(y) = y^3(\tau_1+\tau_2)\sin[(\tau_1+\tau_2)y] + y^2\{[3+(\tau_1+\tau_2)A_2]\cos[(\tau_1+\tau_2)y] + \tau_2 B_2\cos(\tau_2 y)$$
$$+\tau_1 C_2\cos(\tau_1 y)\} - y\{[2A_2+(\tau_1+\tau_2)A_1]\sin[(\tau_1+\tau_2)y] + (2B_2+\tau_2 B_1)\sin(\tau_2 y)$$
$$+(2C_2+\tau_1 C_1)\sin(\tau_1 y)\} + [A_1+(\tau_1+\tau_2)A_0]\cos[(\tau_1+\tau_2)y]$$
$$+(B_1+\tau_2 B_0)\cos(\tau_2 y) + (C_1+\tau_1 C_0)\cos(\tau_1 y) + D_1.$$

We will be using the method described in *Bellman* and *Cooke*[6], *Theorems* 13.3 and 13.7. The method states that if there exists a principal term of the polynomial $H(z)$, then the character of zeros of $H(z)$ is determined by the behavior of $H(z)$ on the imaginary axis. Therefore it requires that we verify first if the principal term $\Phi^{*(\tau_1+\tau_2)}$ (defined in [6], *Theorem* 13.3) satisfies the condition

$$\Phi^{*(\tau_1+\tau_2)}(\epsilon+iy) \neq 0$$

for every y in R and some real ϵ. It is easily checked that in our case $\Phi^{*(\tau_1+\tau_2)}(z) = \cos[(\tau_1+\tau_2)z]$, and thus if we take $\epsilon = 0$, the condition is verified.

Inspection of *Theorems* 13.3 and 13.7 of [6] gives in our case the following necessary and sufficient conditions for the stability of $H(\lambda)$:

(1) The function $G(y)$ has exactly $4(\tau_1+\tau_2)k+3$ real zeros in each interval$[-2k\pi, 2k\pi]$, beginning from some k.

(2) For each such zero y_0 of F, it follows that

$$F(y_0)G'(y_0) > 0.$$

First of all, Consider the degenerate case, i.e. $A_0+B_0+C_0+D_0 = 0$. We see that $G(0) = 0$, and so $F(0) = 0$ This means condition (2) can not be satisfied. Hence $H(\lambda)$ is unstable.

Now assume that $A_0+B_0+C_0+D_0 \neq 0$. Let us start with the *sufficient condition*, and we introduce the following hypotheses:

(3) $G(y)$ has exactly one zero in each of the following intervals:

$$I_1^k = [\frac{2k\pi+\pi/4}{\tau_1+\tau_2}, \frac{2k\pi+3\pi/4}{\tau_1+\tau_2}], \quad I_2^k = [\frac{2k\pi+5\pi/4}{\tau_1+\tau_2}, \frac{2k\pi+7\pi/4}{\tau_1+\tau_2}],$$

where $k \geq k_1$, and G has no other zeros in the interval $[2k\pi/(\tau_1+\tau_2), 2(k+1)\pi/(\tau_1+\tau_2)]$.

(4) $F(y)$ is positive in I_1^k, negative in I_2^k, for $k \geq k_1$.

(5) $G'(y) > 0$ in I_1^k, $G'(y) < 0$ in I_2^k, for $k \geq k_1$.

First, we will prove that conditions (3)-(5) imply conditions (1)and (2), under the hypotheses (a) and (b) of *Theorem* 4.4.5. Since F is even, $G(0) = 0$ and G is odd, it is sufficient when looking at (1) to prove that G has exactly $4(\tau_1 + \tau_3)k + 3$ zeros in $[-2k\pi, 2k\pi]$ for all k large enough, and looking at (2), to prove that $F(y_0)G'(y_0) > 0$ for the zeros in $[-2k\pi, 2k\pi]$.

Proof of (1). We write the interval $[-2k\pi, 2k\pi]$ as the union of $[-2k_1\pi/(\tau_1 + \tau_2), 2k_1\pi/(\tau_1 + \tau_2)]$ and of the intervals $[2l\pi/(\tau_1 + \tau_2), 2(l + 1)\pi/(\tau_1 + \tau_2)]$, $k_1 \leq l \leq k(\tau_1 + \tau_2) - 1$. By using hypothesis (a) of *Theorem* 4.4.5 and condition (3), we count exactly

$$4k_1 + 3 + 4[k(\tau_1 + \tau_2) - k_1] = 4(\tau_1 + \tau_2)k_1 + 3$$

zeros in the interval $[-2k\pi, 2k\pi]$.

Proof of (2). This is a direct consequence of conditions (4) and (5). The next step is to prove that (3)-(5) are true under the conditions of *Theorem* 4.4.5. The proof will be based on the fact that the terms involving the factor y^3 in F, G, G' dominates the remaining terms for y sufficiently large. But because of the presence of $\cos[(\tau_1 + \tau_2)y]$, the domination will only take place in intervals in which $\cos[(\tau_1 + \tau_2)y]$ is far from zero. On the other hand, we will find a zero in intervals at the extremities of which $\cos[(\tau_1 + \tau_2)y]$ takes opposite values and far from zero values.

Let us take $k \geq k_0$; note that the value of $-y^3 \cos[(\tau_1 + \tau_2)y]$ is less than $-B_k/\sqrt{2}$ (resp. greater than $B_k/\sqrt{2}$) on the left (resp. right) end of I_1^k, while A_k is the upper bound for the absolute value of the sum of the remaining terms of $G(y)$. The same estimates are true for I_2^k. Moreover, in the set

$$[\frac{2k\pi}{\tau_1 + \tau_2}, \frac{2(k+1)\pi}{\tau_1 + \tau_2}]/(I_1^k \cup I_2^k),$$

we have $|-y^3 \cos[(\tau_1 + \tau_2)y]| \geq B_k/\sqrt{2}$.

Therefore, G has at least one zero in each of the intervals I_1 and I_2 and has no zero in I, $k \geq k_0$.

A similar argument applied to F shows that $F(y) > 0$ in I_1^k and $F(y) < 0$ in I_2^k, $k \geq k_0$, which is (4).

To complete the verification of (3), we have only to prove (5).

Looking at $G'(y)$, we see that it is a combination of the same functions which appear in F, with other coefficients. Dividing G' by $\tau_1 + \tau_2$, we can define a new A_k' and B_k as before. Thus from the preceding proof, it follows that the condition $B_k > \sqrt{2}A_k'$, $k \geq k_0'$ (for some new constant k_0'), ensures that G' will stay positive in I_1^k and negative in I_2^k. This completes the proof of (3)-(5).

We now show the *necessary condition*. Suppose that (a) does not hold. Then since $G(y)$ is odd, we see that it has less that $4(\tau_1 + \tau_2)k + 3$ zeros in the interval $[-2k\pi, 2k\pi]$ for each k greater than some value. This in turn implies the instability of $H(\lambda)$ by condition(1). Similarly, if (b) does not hold, then $H(\lambda)$ is unstable by condition (2). The proof is complete. □

4.5 Numerical examples

In this section we describe some examples to illustrate some of our results. In the first example there is no treatment considered and parameter values are chosen to fall within the very wide confidence intervals offered by several different papers [17,74,90,107]. In the following example we consider the corresponding treatment with an Michaelis-Menton type function.

4.5.1 An example without chemotherapy treatment

In this section, the example will be of the form

$$\begin{aligned} \dot{x}(t) &= 2(1-a_1)\frac{\lambda_1 x_{\tau_1}}{1+(\frac{gx_{\tau_1}+y_{\tau_1}}{A})^2} - \frac{\lambda_1 x(t)}{1+(\frac{gx(t)+y(t)}{A})^2} - \delta_1 x(t) \\ \dot{y}(t) &= 2(1-a_2)\frac{\lambda_2 y_{\tau_2}}{1+(\frac{x_{\tau_2}+y_{\tau_2}}{A})^2} - \frac{\lambda_1 y(t)}{1+(\frac{x(t)+y(t)}{A})^2} - \delta_2 y(t), \end{aligned} \tag{4.11}$$

where

a_1, a_2 are the apoptosis rates of normal and abnormal cells, respectively.

λ_1, λ_2 are the specific growth rates of the normal and abnormal cells for small densities.

δ_1, δ_2 are the respective differentiation rates.

A is the proliferative limit, which relies on the total(normal and abnormal)stem cell population.

g allows the possibility that the abnormal cells are less sensitive to the standard proliferative limit A, than the normal stem cells.

In this example, the normal population has a delay of 3 days, and the abnormal population has a delay of 45 days. It takes about 600 days for abnormal cells to approach the steady state, and 900 days for healthy cells to be extinct, which means without treatment, cancer cells will win the competition with healthy cells and eventually drive them to extinction($Figure$ 4.3). When we increase the abnormal cell cycle time to 70 days, we observe that the disease grows periodically ($Figure$ 4.4). However, when the abnormal cell cycle time goes beyond the critical value, the highly malignant cancer will eventually give rise to blast crisis ($Figure$ 4.5). Also, it is possible to choose parameters and initial values so that solutions of system (4.11) approach a positive interior steady state, in which we observe an indolent cancer where a higher level cancer coexists with normal cells ($Figure$ 4.6). However, when the abnormal cell cycle time increases to 70 days in this situation, both cell populations still coexist, but grow periodically ($Figure$ 4.7).

4.5.2 An example with chemotherapy treatment

In this section we consider the chemotherapy treatment with the corresponding model in section 4.4.1.

$$\begin{aligned}
\dot{x}(t) &= 2(1-a_1)\frac{\lambda_1 x_{\tau_1}}{1+(\frac{gx_{\tau_1}+y_{\tau_1}}{A})^2} - \frac{\lambda_1 x(t)}{1+(\frac{gx(t)+y(t)}{A})^2} - \delta_1 x(t) - \frac{\eta_1 x(t)u(t)}{1+u(t)} \\
\dot{y}(t) &= 2(1-a_2)\frac{\lambda_2 y_{\tau_2}}{1+(\frac{x_{\tau_2}+y_{\tau_2}}{A})^2} - \frac{\lambda_1 y(t)}{1+(\frac{x(t)+y(t)}{A})^2} - \delta_2 y(t) - \frac{\eta_2 y(t)u(t)}{1+u(t)} \\
\dot{u}(t) &= \Delta - [\gamma + \eta_1 x(t) + \eta_2 y(t)]\frac{u(t)}{1+u(t)},
\end{aligned} \tag{4.12}$$

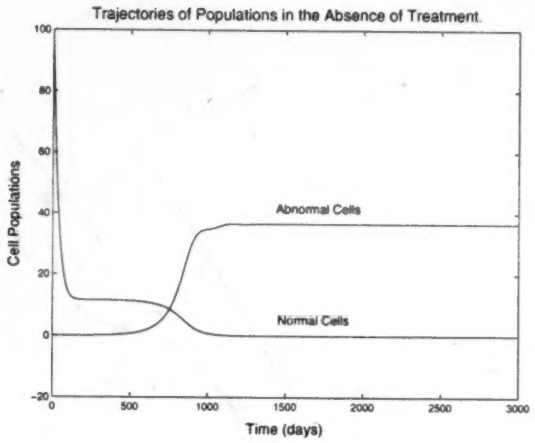

Figure 4.2: A solution for model (4.12) with $a_1 = 0.1, a_2 = 0.05, \lambda_1 = \lambda_2 = 0.2\,day^{-1}, \delta_1 = 0.025\,day^{-1}, \delta_2 = 0.0125\,day^{-1}, \phi_1(t) = 100\,ml, \phi_2(t) = 0.1\,ml, A = 10\,ml, g = 2$.

where

η_1, η_2 represent the cell-killing coefficients to normal cells and abnormal cells respectively.

γ is the loss rate of poison for chemotherapy agents.

Δ is the rate continuous constant infusion of chemotherapy agents.

In this example, we consider the chemotherapy treatment to the model (4.11). To make this model more realistic, we impose certain inequalities among the parameters. It is well known that if no treatment is offered, most of the time leukemia cells out-compete the normal cells independent of initial conditions (see $Figures$4.2-4.7). In order to inhibit the growth of cancer cells and finally destroy them, the chemotherapy agent must be considerably more effective in killing leukemia than in killing normal cells, which means $\eta_2 >> \eta_1$. $Figure$ 4.8 shows that when we apply a higher intensity of the treatment (larger values of η_2 and/or $\gamma^{-1}\Delta$), the heavy drug dosage ultimately causes damage to regrowth and proliferative capabilities of the cancer cells and eventually drive them to extinction even with a high initial value of abnormal cells exhibiting an excellent treatment.

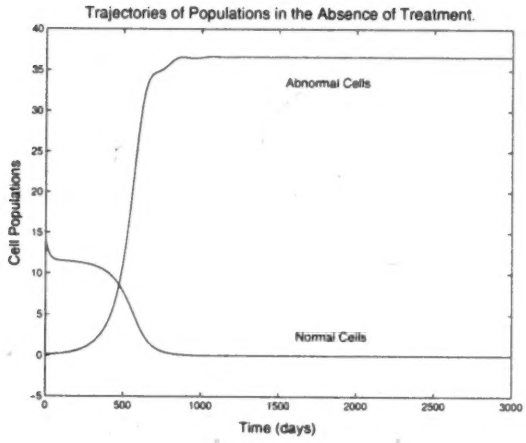

Figure 4.3: A stable steady state with $x = 0$ and $y = \bar{y}$. The parameter values and initial conditions are $a_1 = 0.1, a_2 = 0.05, \lambda_1 = \lambda_2 = 0.2\,day^{-1}, \delta_1 = 0.025\,day^{-1}, \delta_2 = 0.0125\,day^{-1}, \phi_1(t) = 14\,ml, \phi_2(t) = 0.1\,ml, A = 10\,ml, g = 2$. Here the normal population has a delay of 3 days, and the abnormal population has a delay of 45 days.

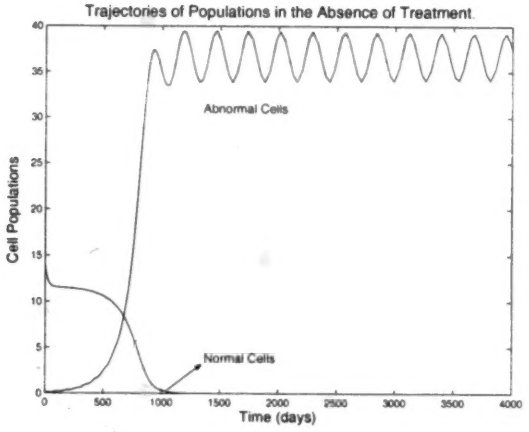

Figure 4.4: A periodic oscillation from the steady state with $x = 0$ and $y = \bar{y}$. Here the parameters and initial conditions are the same as in *Figure* 4.3 and the normal population has a delay of 3 days, and the abnormal population has a delay of 70 days.

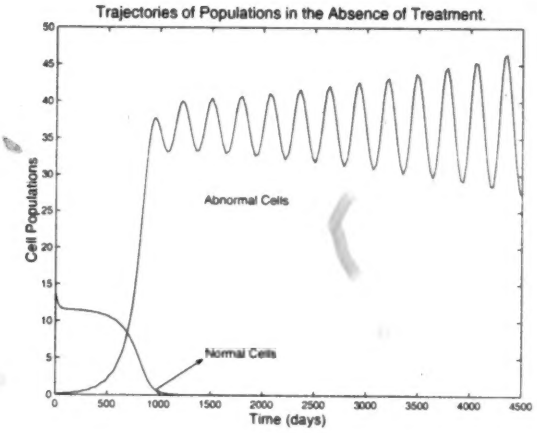

Figure 4.5: An unstable steady state with $x = 0$ and $y = \bar{y}$. Here the parameters initial conditions are the same as in $Figure$ 3 and the normal population has a delay of 3 days, and the abnormal population has a delay of 72.5 days.

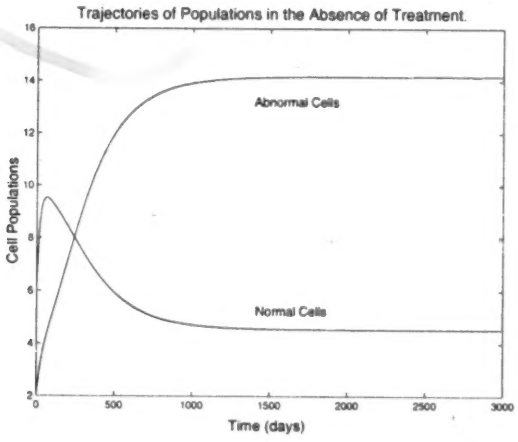

Figure 4.6: A stable interior solution for model (4.12) with $a_1 = 0.1, a_2 = 0.05, \lambda_1 = 0.2\,day^{-1}, \lambda_2 = 0.1\,day^{-1}, \delta_1 = 0.025\,day^{-1}, \delta_2 = 0.02\,day^{-1}, \phi_1(t) = 6\,ml, \phi_2(t) = 2\,ml, A = 10\,ml, g = 2$, Here the normal population has a delay of 3 days, and the abnormal population has a delay of 30 days.

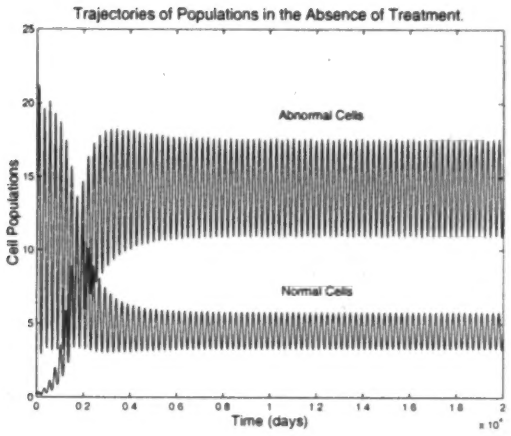

Figure 4.7: A periodic oscillation from the steady state with $x = x^*$ and $y = y^*$. Here the parameters and initial conditions are the same as in *Figure* 4.6 and the normal population has a delay of 70 days, and the abnormal population has a delay of 72.5 days.

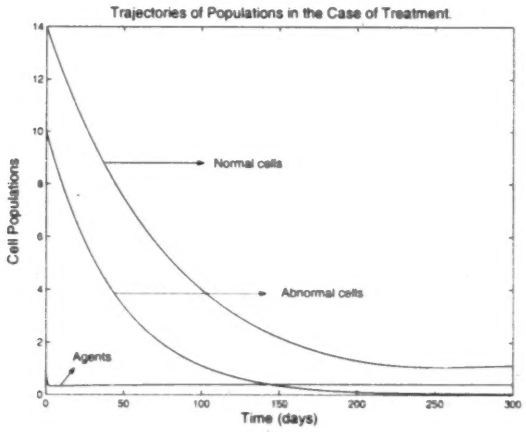

Figure 4.8: A solution for model (4.13) with the same parameter values, initial conditions and delays as in *Figure* 4.3, except $\eta_1 = 0.0002\,day^{-1}, \eta_2 = 0.04\,day^{-1}, \gamma = 8\,day^{-1}, \Delta = 64\,ml\,day^{-1}, \phi_2(t) = 2\,ml, u_0 = 9\,ml$.

4.6 Discussion

Chronic myeloid leukemia is characterized by the abnormal growth of relatively mature myeloid cells. Initially in chronic myeloid leukemia, there is a gradual increase in mature, abnormal myeloid cells in the bone marrow. The number of leukemic cells increases slowly at first, which is referred to as the chronic phase, but these cells invariably begin to increase more rapidly and/or include less mature cells, resulting in the accelerated or blastic phase. Eventually, the leukemia becomes completely resistant to treatment and the bone marrow becomes overburdened with large numbers of immature white blood cells known as "blasts". Generally, the massive hyperplasia is referred to the acceleration phase and blastic crisis referred to the acute phase.

This chapter is based on the work (Jamieson et al [52]), in which it is shown biomedically that the progression of CML to blast crisis is supported by self-renewing leukemic progenitor cells. Our purpose here is to justify this work mathematically and to try to give a plausible explanation of the dynamical progression of the disease. We know that the abnormal cells grow at the expense of the normal cells. Generally, CML cells do not grow faster than normal cells, but they persist longer or divide more often during their lifetime. At some point where the abnormal cells outnumber the normal cells, there appears to be a stable state for a period of time before it becomes unstable. From a mathematical modeling perspective, this immediately causes us to search for a slow moving variable. The time delay needed for a cell to reproduce could be altered by the same mutation that causes the growth advantage in CML.

In this chapter, we assumed in chronic myeloid leukemia a downstream progenitor a granulocyte-macrophage progenitor can acquire self-renewal capacity with the same properties as the standard G_0 in [65] and the progression of CML to blast crisis is supported by the self-renewing leukemic progenitor cells. We assumed that the normal and abnormal cells have different cell cycle times, and cancer cells have a longer cell cycle time than that of normal cells. The model described both the normal process and that in chronic myelogenous leukemia. It demonstrated that the abnormal cell cycle time did give rise to the oscillatory solutions to the model system and showed how the CML cells can ultimately outnumber the normal cells and how this process can be very slow. Compared with the

normal cell cycle time, if the abnormal cell cycle time is less than a threshold number, the disease stays stable; when the delay increases beyond the critical number, an oscillatory instability occurred. At the critical number, the disease grew periodically. With regard to the model system, sufficient conditions for the stability of all equilibria for the complicated system were obtained.

The model should be helpful in designing experiments to better define the abnormalities of proliferation in CML. With regard to the cancer chemotherapy, stability switching is a very important issue in the design of a drug protocol. The results we obtained here can be used to clinical advantage. If we are certain that our parameters are in the stability switch region and the equilibrium is unstable, then in this case it may be possible to stabilize the cancer-free equilibrium by increasing or decreasing the delay τ_2. Moreover, by comparing the treatment case to the no treatment case, it is easy to see that the chemotherapy agents did inhibit the growth of cancer cells and enhanced the recovery of heathy cells. (Compare *Theorem* 4.3.2 to *Theorem* 4.4.1-4.4.2, and *Theorem* 4.3.3 to *Theorem* 4.4.3-4.4.4). Finally, we note that because of the complexity of the model system, global stabilities of the equilibria are very difficult to carry out analytically.

The immune response might also be an obvious place to look for this slowly moving variable. Other less promising yet reasonable places to look for this variable include the slow exhaustion of the stem cell niche (a physical space that stem cells occupy when receiving growth factors), as well as the idea of a continuous, though very low, mutation rate. In the future, we will consider and include these factors into our model to study the development of chronic myeloid leukemia. Age-structure models might also be a good modeling approach to study chronic myeloid leukemia. The model considered here is a general one which includes many special cases. We are aware that models are not the purposes; they are tools for us to better understand the underlying biological process and dynamics, and we hope in that sense, they may be of some use.

5

A Cancer Treatment of Cycle-Specific Chemotherapy to the G_0 Model

5.1 Introduction

The standard G_0 model was developed by Mackey [65], in which he worked on the haematopoietic stem cell population (HSC) in order to calculate the steady state parameters characterizing the HSC populations, such as the differentiation rate, the rate of cell re-entry from G_0 back into the proliferative phase, and the rate of apoptosis. The G_0 model takes the form:

$$\begin{aligned} \dot{P}(t) &= -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau \\ \dot{N}(t) &= -[\beta(N) + \delta]N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau, \end{aligned}$$

where $P(t)$ represents the density of proliferating phase cells, and $N(t)$, the density of resting phase cells. τ is the time required for a cell to traverse the proliferative phase, and the resting to proliferative phase. Feedback rate β is taken to be a function of P, N, or $P + N$ [65].

The purpose of [65] is to understand how the HSC population carries out the cellular production over the course of a lifetime and thus the kinetics of HSC populations. In order

to better understand the standard G_0 model properties in [65], we describe our modeling assumptions below for this chapter.

The cell cycle is the process between two cell divisions (or mitosis)[27,56] and at any time, stem cells may be involved in one of three activities. They may remain "resting" in the so-called G_0 stage. In this stage, the cells neither proliferate nor initiate any further cellular differentiation and just remain in their current compartment. Alternatively, when a proper stimulus arises, some of these cells in the G_0 stage will be "triggered off" to enter into a cell cycle to begin a self-renewal process (at a rate α_3) involving four phases. The first, called the G_1 phase, is the first "gap" (hence the "G") in the reproductive process before DNA synthesis (S). While in this phase, the cell is busy reproducing cell components that will be required by the daughter cells resulting from the reproductive cell cycle. G_1 could last as long as 48 hours and is the longest phase of the cycle. After Gap1, the cell enters the synthesis phase and new DNA, as well as a number of proteins, are synthesized. During synthesis, the chromosomal DNA is copied into two sister chromatids. This phase may last between 8 and 20 hours. After synthesis, the cell enters another gap phase, called G_2 or Gap2, during which more proteins are produced, the material used for the cell membrane is created, and chromosomes are formed by the super-coiling of the DNA. Finally, the cell moves on to mitosis (M), during which the cell will actually divide into two daughter cells. Mitosis is the shortest phase of all, lasting up to one hour. The duration of the cell cycle is very much dependent on the type of cell and its growth conditions[104]. In general, each daughter cell is given one of the two sister chromatids formed earlier during DNA synthesis. Hence, after a time delay τ, two cells re-enter the compartment as a result of one cell self-renewing. Some cells will die (at a rate δ_i, $i = 1, 2$) during this proliferation process. This type of cellular death is called apoptosis. Finally, the third possibility is that the cells leave a given compartment (at a rate δ_3) and begin the process of cellular differentiation. The model is known as the G_0 model and is illustrated in $Figure$ 5.1.

In cancer treatment today, chemotherapy treatment has demonstrated a definite capacity for controlling disseminated metastatic cancer and is widely used. Unfortunately, drugs in cancer chemotherapy kill normal as well as cancerous cells. Naturally it is desirable to kill as many cancerous cells as possible while sparing as many normal cells as

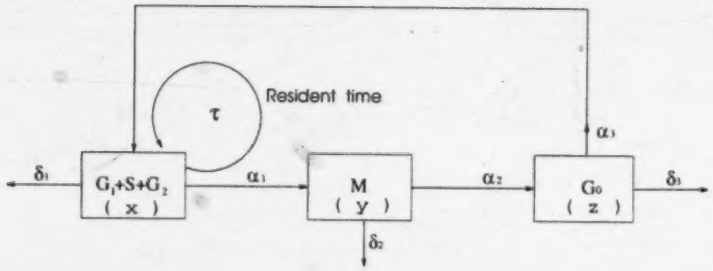

Figure 5.1: The model for cell growth illustrates how a cell may either remain in the G_0 resting phase, begin to differentiate into different types of cells, or reproduce. Reproduction is a four stage process beginning with the Gap1 phase(G_1), moving to DNA synthesis(S), the second gap phase(G_2), and finally, mitosis(M).

possible. One way of accomplishing this goal is by taking advantage of the fact that many chemotherapeutic drugs are cycle-specific: they only destroy cells in the specific phases of their cycle. In the cell synchronization method the cancerous cells are first synchronized by one drug. When nearly all the cancerous cells reach the desirable phase, they are treated with a second cycle-specific drug. This kills the maximum number of cancer cells while sparing large numbers of normal cells. Some examples of these types of drugs are Cytosine Arabinoside (Ara-C), 5-fluorouracil and Prednisone which work in the G_1 and S phases of the cell-cycle and Vincristine, Paclitaxel and Bleomycin which work in the M phase of the cell-cycle [56]. Hence the cell is disabled from continuing in the cell cycle, and thus the drugs stop the cell proliferation and allow a natural death of cells due to the immune system [104]. The object of the model in this chapter is to model the effects and interactions between cancer cells and cells of the immune system, clearly differentiating between phases for subsequent treatment with the M phase in the G_0 compartment. Taking the cycle-specificity of drugs into consideration, it is therefore, very natural to subdivide the cancer population into its different stages, which will make it easier to control and model how the drug acts on the different stages of the cell cycle.

Some of the more recent work done with mathematical models of cycle-specific chemotherapy is by Webb [106]. He develops both linear and nonlinear models of cycle-specific chemotherapy. The advantage of periods of dose with shorter duration are invested

in the case of the linear model. Another work of interest is by Birkhead et al. [7] in which a four-compartment linear system is developed to model the cycling, resistant, and resting cells. Their results are limited to a few numerical calculations on four specific types of treatments. Swan[101] also examines cycle-specific chemotherapy in his review article. Particularly, he concentrates on age-structured models which take into account the age of the cells in each compartment of the cell cycle. He also studies an age-structured chemotherapeutic model of acute myeloid leukemia. The fact is that in the above articles only chemotherapy is considered. Kirschner and Panetta [55] included the immune system into a mathematical model to study immunotherapy as an alternative to chemotherapy. In [104] the authors model the cycle-specific chemotherapy that includes the immune system but excludes the resting stage. In their paper, they study the interaction of tumor cells and drug with the immune system and show that the stability of fixed points may depend on the delay.

The model we propose is an extension of the models above, especially, the model developed by Villasana and Radunskaya [104]. However, we find that the model in [104] is wrong in the development of one delayed term in the model, which will make solutions of the system negative in positive time. Therefore, we correct their model and include the immune system and the quiescent stage into the model. The inclusion of the resting phase into the model in [104] makes it a standard G_0 model developed by Mackey [65]. Here, we subdivide the population in the G_0 model into different stages to account for the cycle-specificity of the drugs. The consideration of a resting compartment is very important and it is worth exploring in more detail since it is known that the cells in this phase escape the action of cycle-specific cytotoxic agents and that approximately only 20 per cent of the cells are cycling in the normal state [104].

Following the assumptions made in [104] and the additional assumptions made for the new model, we will work on the new model to answer the following questions of chemotherapy such as: will the cancer grow or decay, how will the major parameters affect the outcome, and what is the optimal regimen to deliver the drugs? In this chapter, we will present the new model in section 5.2, and discuss the stability of cancer-free equilibria with/without immune suppression and/or in the case of drugs in section 5.4. In section 5.5,

we study the Hopf bifurcation and finally conclude with numerical results and a discussion.

5.2 The model

We take as our model of cancer treatment by chemotherapy a system of delayed differential equations, where $x(t)$ represents the density of cancer cells during the interphase (namely, $G_1 + S + G_2$) at time t, $y(t)$ is the density of cancer cells during the mitotic phase at time t, $z(t)$ is the density of cancer cells during the resting phase at time t, $I(t)$ is the density of lymphocytes at time t, and $u(t)$ is the concentration of chemotherapy drug present at time t. τ is the resident time of cells in the interphase. The model then takes the form

$$\begin{aligned}
\dot{x}(t) &= \alpha_3 z(t) - \alpha_1 x(t) - (\delta_1 + k_1 I(t))x(t) \\
\dot{y}(t) &= \alpha_1 x(t-\tau) - (\alpha_2 + \delta_2 + k_2 I(t))y(t) - k_4(1 - e^{-k_5 u(t)})y(t) \\
\dot{z}(t) &= 2\alpha_2 y(t) - (\alpha_3 + \delta_3 + k_3 I(t))z(t) \\
\dot{I}(t) &= k + \frac{\rho I(t)(x+y+z)^n}{a + (x+y+z)^n} - (\delta_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))I(t) - k_6(1 - e^{-k_7 u(t)})I(t) \\
\dot{u}(t) &= -\gamma u(t),
\end{aligned}$$

with initial conditions

$$x(t) = \phi_1(t) \geq 0,\ t \in [-\tau, 0]\,, y(0) = y_0 \geq 0\,, z(0) = z_0 \geq 0\,, I(0) = I_0 > 0\,, u(0) = u_0 \geq 0.$$

The constants in this system may be interpreted as follows:

δ_i, $i = 1, 2, 3, 4$, are the proportions of natural death or apoptosis of x, y, z and I for small densities.

α_1 represents the rate at which cells flow into the mitosis phase.

α_2 represents the rate at which cells flow into the resting compartment.

α_3 represents the rate at which cells cycle or reproduce.

c_i, $i = 1, 2, 3$, represent losses from encounters of cancer cells with immune cells (lymphocytes).

ρ represents the proportion of the nonlinear growth of lymphocytes due to stimulus by the cancer cells.

a determines the speeds at which the lymphocytes, in the absence of stimulation, reach

their saturation level.

k is the growth rate of the lymphocytes in the absence of cancer cells.

k_i, $i = 1, 2, 3$, are the rates at which lymphocytes destroy the cancer cells in different phases.

k_i, $i = 4, 5, 6, 7$, are the proportions of chemotherapy drugs which eliminate cancer cells and lymphocytes.

γ represents the proportion of decay of the drugs.

All constants are positive. The cancer cells reside in the cycle for a certain period of time τ before entering into the resting stage. Thus we have the term $x(t-\tau)$ in the system. With respect to high densities of drugs, we know that the drug interferes with cancer cells in mitosis where they die naturally when they fail to complete the cycle. So we assume that once the drug encounters the cancer cell, the cancer cell is taken out of the cycle and can no longer proliferate. This is modeled by the term $-k_4(1-e^{-k_5 u})y$, but there are other curves that describe a similar feature(see [79]). Biologically, this treatment term means that when no drugs are applied ($k_5 = 0$), there are no effects on the cancer cell population since $1 - e^{-k_5 u} = 0$. Further, k_4 represents the intensity of the treatment. In this new model, we assume that the resting cells are not affected by the drugs but immune cells will attack them. This assumption comes from the fact that faster proliferating cells are more sensitive to the drugs, while the cells in the resting phase escape the action of cycle-specific cytotoxic agents [104]. For other assumptions for the model, the reader is referred to [104]. The purpose of this chapter is to study the cycle-specificity of chemotherapy, therefore the treatment terms are assumed different from the form used in the previous chapters.

Finally, we note that to the best of our knowledge this is the first model to incorporate both chemotherapy ($u(t)$) and immunotherapy ($I(t)$) effects.

5.3 Nondimensionalization

Following similarly as in [104], we nondimensionalize the system and write

$$\bar{t} = \frac{t}{day}, \quad \bar{x} = \frac{x}{x(0)}, \quad \bar{y} = \frac{y}{x(0)}, \quad \bar{z} = \frac{z}{z(0)}, \quad \bar{I} = \frac{I}{I(0)}, \quad \bar{u} = \frac{u}{u(0)}, \quad s = \frac{z(0)}{x(0)},$$

$$\bar{k}_1 = k_1 I(0), \quad \bar{k}_2 = k_2 I(0), \quad \bar{k}_3 = k_3 I(0), \quad \bar{k}_5 = k_5 u(0), \quad \bar{k}_7 = k_7 u(0),$$

$$\bar{a} = a/x^n(0), \quad \bar{c}_1 = c_1 x(0), \quad \bar{c}_2 = c_2 x(0), \quad \bar{c}_3 = c_3 z(0), \quad \bar{k} = k/I(0),$$

where $x(0) = y(0)$ are initial values. By renaming the variables $\bar{t}, \bar{x}, \bar{y}, \bar{z}, \bar{I}, \bar{u}$ to t, x, y, z, I, u respectively, and the parameter values $\bar{k}, \bar{a}, \bar{k}_i, \bar{c}_j$ to k, a, k_i, c_j respectively, $i = 1-7$; $j = 1-3$, then all the new parameters and variables do not have dimensions. Now we will work with the non-dimensionalized model from this point on:

$$\begin{aligned}
\dot{x}(t) &= s\alpha_3 z(t) - \alpha_1 x(t) - (\delta_1 + k_1 I(t))x(t) \\
\dot{y}(t) &= \alpha_1 x(t-\tau) - (\alpha_2 + \delta_2 + k_2 I(t))y(t) - k_4(1 - e^{-k_5 u(t)})y(t) \\
\dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \delta_3 + k_3 I(t))z(t) \\
\dot{I}(t) &= k + \frac{\rho I(t)(x + y + sz)^n}{a + (x + y + sz)^n} - (\delta_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))I(t) - k_6(1 - e^{-k_7 u(t)})I(t) \\
\dot{u}(t) &= -\gamma u(t),
\end{aligned} \tag{5.1}$$

with initial conditions

$$x(t) = \phi_1(t) \geq 0,\ t \in [-\tau, 0], y(0) = y_0 \geq 0, z(0) = z_0 \geq 0, I(0) = I_0 > 0, u(0) = u_0 \geq 0.$$

5.4 Stability results

We first determine the type of dynamics that can arise in the system without the presence of the drug and then study the case with drugs. Hence we begin by analyzing the simplest case: a drug-free model in a non-delay case in the absence of an immune response.

5.4.1 Drug-free model in a non-delay case in the absence of an immune response

In this subsection, we shall study the drug-free model in a non-delay case without an immune response. Necessary and sufficient conditions that guarantee the stability of the cancer-free equilibrium are obtained. Also, a necessary condition for cancer growth is

obtained. In this case the equations are a simple set of ordinary differential equations:

$$\begin{aligned}
\dot{x}(t) &= -(\alpha_1+\delta_1)x(t) + 0y(t) + s\alpha_3 z(t) \\
\dot{y}(t) &= \alpha_1 x(t) - (\alpha_2+\delta_2)y(t) + 0z(t) \\
\dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3+\delta_3)z(t),
\end{aligned} \tag{5.2}$$

with initial values

$$x(0) = x_0, y(0) = y_0, z(0) = z_0.$$

This is a linear system with the only equilibrium being $E_0(0,0,0)$. The Jacobian matrix about this equilibrium is

$$\begin{bmatrix} -(\alpha_1+\delta_1) & 0 & s\alpha_3 \\ \alpha_1 & -(\alpha_2+\delta_2) & 0 \\ 0 & 2s^{-1}\alpha_2 & -(\alpha_3+\delta_3) \end{bmatrix},$$

and the characteristic equation is

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0,$$

where

$$\begin{aligned}
a_2 &= \alpha_1+\delta_1+\alpha_2+\delta_2+\alpha_3+\delta_3 \\
a_1 &= (\alpha_1+\delta_1)(\alpha_2+\delta_2) + (\alpha_2+\delta_2)(\alpha_3+\delta_3) + (\alpha_3+\delta_3)(\alpha_1+\delta_1) \\
a_0 &= (\alpha_1+\delta_1)(\alpha_2+\delta_2)(\alpha_3+\delta_3) - 2\alpha_1\alpha_2\alpha_3 \\
&= \alpha_1\alpha_2(\delta_3-\alpha_3) + (\alpha_3+\delta_3)(\alpha_1\delta_2+\alpha_2\delta_1+\delta_1\delta_2).
\end{aligned} \tag{5.3}$$

Clearly, a_2, a_1 are positive and $a_2a_1 > a_0$. By the Routh-Hurwitz criteria , necessary and sufficient conditions for λ to have negative real parts become $a_0 > 0$.

As a result, we have the following lemma.

Lemma 5.4.1 *The cancer-free equilibrium E_0 of system (5.2) is locally asymptotically stable if and only if $a_0 > 0$.*

Note that α_3 represents the rate at which cells in the resting phase enter into their cell cycles to reproduce cells, and δ_3 is the proportion of cells which die naturally in the resting phase. It is easy to see from *Lemma* 5.4.1 that a necessary condition for the extinction of all cancer

cells is just that the death rate is greater than the reproduction rate ($\delta_3 > \alpha_3, i.e.\, a_0 > 0$) in the resting phase, that is, the control of the death rate of cells in the resting compartment is sufficient to inhibit the growth of cancer.

Based on *Lemma* 5.4.1, a necessary condition for the cancer growth is $a_0 \leq 0$, which implies that the cancer growth rate in the resting phase must exceed its death rate ($\alpha_3 > \delta_3$). In general, all cancer cells eventually lose their ability to respond to signals to divide or die [104]. Therefore, cancer cells accumulate, competing with normal cells for nutrients and encroaching on the space and territory of other cells (thus, $\alpha_3 > \delta_3$). *Lemma* 5.4.1 implies that cancer cells will eventually win the competition and begin to grow in the absence of any treatment.

5.4.2 Drug-free model when $\tau > 0$ in the absence of an immune response

In this subsection, We are interested in studying how the conditions for the cancer growth or extinction are varied for positive values of the delay τ. When we add the effect of the delay in the model, we obtain

$$\begin{aligned} \dot{x}(t) &= -\alpha_1 x(t) - \delta_1 x(t) + s\alpha_3 z(t) \\ \dot{y}(t) &= \alpha_1 x(t-\tau) - (\alpha_2 + \delta_2) y(t) \\ \dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \delta_3) z(t). \end{aligned} \tag{5.4}$$

Note that system (5.2) in section 5.4.1 corresponds to the special case when $\tau = 0$. As before the only equilibrium of this system is the cancer-free point $E_0(0,0,0)$. For the determination of stability in the case of delayed differential equations, we linearize the system about the equilibrium and consider exponential solutions which are characterized by the eigenvalues for exponents of these solutions. The characteristic equation for this system about the equilibrium E_0 is given by

$$\begin{vmatrix} \lambda + \alpha_1 + \delta_1 & 0 & -s\alpha_3 \\ -\alpha_1 e^{-\lambda\tau} & \lambda + \alpha_2 + \delta_2 & 0 \\ 0 & -2s^{-1}\alpha_2 & \lambda + \alpha_3 + \delta_3 \end{vmatrix} = 0,$$

that is,

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + 2\alpha_1\alpha_2\alpha_3 - 2\alpha_1\alpha_2\alpha_3 e^{-\lambda\tau} =: P_1(\lambda) + Q_1(\lambda)e^{-\lambda\tau} = 0, \tag{5.5}$$

where a_0, a_1, a_2 are given by (3.5).

There are many ways in which we can determine if there is a root λ of the characteristic equation with positive real part. Geometric arguments can be used to establish the stability of an equilibrium, such as those used by Mahaffy in [66], where the argument principle is used to count the number of zeros of characteristic equation (5.5) on the right hand side of the complex plane. However, in our case we will resort to some results by Cooke and van den Driessche in *Theorem* 1 of [18].

They define the function

$$F(y) = |P_1(iy)|^2 - |Q_1(iy)|^2,$$

and analyze the function $F(y)$, giving conditions under which equation (5.5) is stable as a function of τ. They also give conditions under which stability changes may occur as the delay τ is increased and show that in these cases the equilibrium is unstable for large enough τ. In short, they showed: (a) Suppose that $F(y) = 0$ has no positive roots. Then if (5.5) is stable at $\tau = 0$ it remans stable for all $\tau \geq 0$, whereas if it is unstable at $\tau = 0$ it remains unstable for all $\tau \geq 0$. (b) Suppose that $F(y) = 0$ has at least one positive root and that each positive root is simple. Then as τ increases, stability switches may occur. There exists a positive $\bar{\tau}$ such that (5.5) is unstable for all $\tau > \bar{\tau}$. As τ varies from 0 to $\bar{\tau}$, and at most a finite number of stability switches may occur.

Following the steps in this theorem it is straightforward to check the stability of the equilibrium and find the conditions for cancer growth. In this case $F(y)$ is found to be:

$$F(y) = y^6 + m_2 y^4 + m_1 y^2 + m_0,$$

where

$$\begin{aligned} m_2 &= a_2 - 2a_1, \\ m_1 &= {a_1}^2 - 2a_2(a_0 + 2\alpha_1\alpha_2\alpha_3), \\ m_0 &= {a_0}^2 + 4a_0\alpha_1\alpha_2\alpha_3. \end{aligned}$$

Let $y^2 = x$. Then $F(y)$ becomes

$$F_1(x) = x^3 + m_2x^2 + m_1x + m_0. \tag{5.6}$$

In order to examine the stability of the steady states, we employ a lemma in [54] quoted here.

Lemma 5.4.2 *Define*

$$\Delta = \frac{4}{27}{m_1}^3 - \frac{1}{27}{m_2}^2{m_1}^2 + \frac{4}{27}{m_2}^3m_0 - \frac{2}{3}m_2m_1m_0 + {m_0}^2.$$

Suppose that $m_0 > 0$. Then:

(I) Necessary and sufficient conditions for the cubic equation (5.6) to have at least one simple positive root for x are:

(i)either (a) $m_2 < 0$, $m_1 \geq 0$ and ${m_2}^2 > 3m_1$, or (b) $m_1 < 0$;

and

(ii) $\Delta < 0$.

(II) Necessary and sufficient conditions for the cubic equations (5.6) to have no positive real roots for x are either one of the following,

(i) $3m_1 \geq {m_2}^2$,

(ii) ${m_2}^2 > 3m_1$ and $\Delta > 0$ or

(iii) ${m_2}^2 > 3m_1$, $\Delta \leq 0$, $m_2 > 0$ and $m_1 > 0$.

Based on *Lemmas* 1 and 2 and methods found in [18], we obtain the following stability theorems.

Theorem 5.4.1 *For system (5.4), suppose that ${m_2}^2 > 3m_1$, $\Delta \leq 0$, $m_2 > 0$ and $m_1 > 0$. Then*

1) if $a_0 > 0$, the stability of equilibrium E_0 is independent of delay τ and it remains stable for all $\tau \geq 0$,

2) if $a_0 < 0$ and $m_0 > 0$, the stability of equilibrium E_0 does not depend on τ and it remains unstable for all $\tau \geq 0$.

It follows from *Lemma* 5.4.1 and *Theorem* 5.4.1 that there is a certain case in which the condition for cancer growth or extinction will remain unchanged even if we add the delay in the corresponding model. In such a case, we say the delay is harmless for the stability of system.

Theorem 5.4.2 *For system (5.4), assume that either (a)* $m_2 < 0$, $m_1 \geq 0$ *and* $m_2{}^2 > 3m_1$, *or (b)* $m_1 < 0$ *and* $\Delta < 0$. *Then there exists a positive* $\bar{\tau}$ *such that*
(i) if $a_0 > 0$, *the cancer-free equilibrium* E_0 *remains stable for* $0 \leq \tau < \bar{\tau}$, *and becomes unstable for all* $\tau > \bar{\tau}$,
(ii) if $a_0 \leq 0$ *and* $m_0 > 0$, *the cancer-free equilibrium* E_0 *remains unstable for* $0 \leq \tau < \bar{\tau}$, *becomes stable when* $\tau > \bar{\tau}$.
Furthermore, in both cases, the cancer-free equilibrium will become unstable when the delay gets sufficiently large.

Theorem 5.4.2 shows that stability switches occur in certain situations. In cancer chemotherapy stability switching is a very important issue in the design of a drug protocol. We must keep in mind that in many cases the drugs prevent cells from continuing through their cell cycle, thus trapping them at some point during interphase, where the cells die from natural causes. This effect can be interpreted as an increase in the delay τ (see (ii) of *Theorem* 4.5.2). But as we have seen here this trapping may have adverse effects, since it may cause the cancer free fixed points to become unstable when they were stable initially (see (i) of *Theorem* 4.5.2). On the other hand, the same properties can be used to the clinicians advantage, if we are certain that our parameters are in the stability switch region and the equilibrium is unstable (see (ii) of *Theorem* 4.5.2). In this case, it may be possible to use the same trapping mechanism to stabilize the cancer-free equilibrium.

5.4.3 Drug-free model in a non-delay case with immune suppression

In this subsection, We will add the effect of immune suppression to study how lymphocytes will change the dynamical behavior of cancer cells when $\tau = 0$. New conditions for cancer growth or extinction that involve the immune suppression parameter terms will be obtained.

When adding immune suppression, the system becomes:

$$\begin{aligned}
\dot{x}(t) &= -(\alpha_1+\delta_1)x(t) + s\alpha_3 z(t) - k_1 x(t) I(t) \\
\dot{y}(t) &= \alpha_1 x(t) - (\alpha_2+\delta_2)y(t) - k_2 y(t) I(t) \\
\dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3+\delta_3)z(t) - k_3 z(t) I(t) \\
\dot{I}(t) &= k + \frac{\rho I(t)(x+y+sz)^n}{a+(x+y+sz)^n} - (c_1 x(t) + c_2 y(t) + c_3 z(t) + \delta_4) I(t). \qquad (5.7)
\end{aligned}$$

Note that $E_1(0,0,0,k/\delta_4)$ is an equilibrium of this system with zero cancer level and a positive immune level. In general, there will be other fixed points, but this fixed point is of particular interest since it represents a caner-free state. The Jacobian matrix about E_1 is

$$\begin{bmatrix}
-(\alpha_1+\delta_1+k_1k/\delta_4) & 0 & s\alpha_3 & 0 \\
\alpha_1 & -(\alpha_2+\delta_2+k_2k/\delta_4) & 0 & 0 \\
0 & 2s^{-1}\alpha_2 & -(\alpha_3+\delta_3+k_3k/\delta_4) & 0 \\
-c_1k/\delta_4 & -c_2k/\delta_4 & -c_3k/\delta_4 & -\delta_4
\end{bmatrix}.$$

Clearly, $\lambda = -\delta_4$ is an eigenvalue and the remaining eigenvalues are given by the solutions to the characteristic equation

$$\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0, \qquad (5.8)$$

where

$$\begin{aligned}
b_2 &= \alpha_1+\delta_1+\alpha_2+\delta_2+\alpha_3+\delta_3+\frac{k}{\delta_4}(k_1+k_2+k_3) \\
b_0 &= (\alpha_1+\delta_1+\frac{k_1k}{\delta_4})(\alpha_2+\delta_2+\frac{k_2k}{\delta_4})(\alpha_3+\delta_3+\frac{k_3k}{\delta_4}) - 2\alpha_1\alpha_2\alpha_3 \\
&= \alpha_1\alpha_2(\delta_3+\frac{k_3k}{\delta_4}-\alpha_3) + (\alpha_3+\delta_3+\frac{k_3k}{\delta_4})(\alpha_1\alpha_2 \\
&+ \alpha_1(\delta_2+\frac{k_2k}{\delta_4}) + \alpha_2(\delta_1+\frac{k_1k}{\delta_4}) + (\delta_1+\frac{k_1k}{\delta_4})(\delta_2+\frac{k_2k}{\delta_4})), \qquad (5.9)
\end{aligned}$$

$$b_1 = (\alpha_1+\delta_1+\frac{k_1k}{\delta_4})(\alpha_2+\delta_2+\frac{k_2k}{\delta_4}) + (\alpha_2+\delta_2+\frac{k_2k}{\delta_4})(\alpha_3+\delta_3+\frac{k_3k}{\delta_4}) + (\alpha_3+\delta_3+\frac{k_3k}{\delta_4})(\alpha_1+\delta_1+\frac{k_1k}{\delta_4}).$$

Obviously, b_2, b_1 are positive and and $b_2b_1 > b_0$. By the Routh-Hurwitz criteria, necessary and sufficient conditions for λ to have negative real parts become $b_0 > 0$.

As a result, we have the following.

Lemma 5.4.3 *For system (5.7), the equilibrium E_1 is locally asymptotically stable if and only if $b_0 > 0$.*

Biological implications from *Lemma* 5.4.3 are given below.

1) Note that α_3 represents the rate at which cells in the resting phase begin to go into their cell cycles to reproduce, and δ_3 is the proportion of the natural death of cells in the resting phase. Comparing with *Lemma* 5.4.1, it is easy to see from *Lemma* 5.4.3 that a necessary condition ($\delta_3 > \alpha_3$) for the cancer extinction in the absence of any treatments will also guarantee the extinction of cancer cells also with the presence of immune suppression.

2) k represents the growth rate of lymphocytes, k_3 represents the rate at which lymphocytes destroy the cancer cells in the resting phase, and δ_4 is the the natural death rate of lymphocytes in the resting compartment. When we include the immune suppression into the model, we find that it will greatly help to inhibit the further growth of cancer cells since conditions for cancer extinction easily are obtained (see the first term of b_0).

3) If lymphocytes are very effective in destroying the cancer cells in the resting phase (sufficiently high value of k_3) with a lower natural death rate (sufficiently small value of δ_4), then it becomes easy to obtain the condition for extinction of cancer cells ($b_0 > 0$) in all phases(sufficiently high value of $kk_3\delta_4^{-1}$ such that $\delta_3 + kk_3\delta_4^{-1} > \alpha_3$, i.e. $b_0 > 0$).

4) From *Lemma* 5.4.3, we see that a necessary condition for the cancer growth is $b_0 \leq 0$, which implies that cancer cells always intend to win the competition with normal cells and will begin to grow($\alpha_3 > \delta_3$) without any treatment.

5.4.4 Drug-free model when $\tau > 0$ with immune suppression

When we add the effect of the delay in the drug-free model with immune suppression, we obtain

$$\begin{aligned}
\dot{x}(t) &= -\alpha_1 x(t) - \delta_1 x(t) + s\alpha_3 z(t) - k_1 x(t) I(t), \\
\dot{y}(t) &= \alpha_1 x(t-\tau) - (\alpha_2 + \delta_2) y(t) - k_2 y(t) I(t), \\
\dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \delta_3) z(t) - k_3 z(t) I(t), \\
\dot{I}(t) &= k + \frac{\rho I(t)(x+y+sz)^n}{a + (x+y+sz)^n} - (c_1 x(t) + c_2 y(t) + c_3 z(t) + \delta_4) I(t). \quad (5.10)
\end{aligned}$$

Again, E_1 is an equilibrium and its analysis is similar to the case of section 5.4.2 though computations are complicated by more terms. This system has the same equilibria as the system described in section 5.4.3, but again we focus on the cancer free equilibrium E_1.

In the case of a positive delay, the characteristic equation for the linearized equation about the fixed point E_1 is given by:

$$\begin{vmatrix} \lambda+\alpha_1+\delta_1+k_1k/\delta_4 & 0 & -s\alpha_3 & 0 \\ -\alpha_1 e^{-\lambda\tau} & \lambda+\alpha_2+\delta_2+k_2k/\delta_4 & 0 & 0 \\ 0 & -2s^{-1}\alpha_2 & \lambda+\alpha_3+\delta_3+k_3k/\delta_4 & 0 \\ c_1k/\delta_4 & c_2k/\delta_4 & c_3k/\delta_4 & \lambda+\delta_4 \end{vmatrix} = 0.$$

Clearly, $\lambda = -\delta_4$ is an eigenvalue and the remaining eigenvalues are given by the solutions to the characteristic equation

$$\begin{aligned} H(\lambda) &= P_2(\lambda) + Q_2(\lambda)e^{-\lambda\tau} \\ &= \lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 + 2\alpha_1\alpha_2\alpha_3 - 2\alpha_1\alpha_2\alpha_3 e^{-\lambda\tau}, \end{aligned}$$

where b_0, b_1, b_2 are given by (5.9).

Geometric arguments using the argument principle can be used to establish the stability of a given fixed point by counting the number of zeros of $H(\lambda)$ on the right hand side of the complex plane[66]. The argument is based on the relative orientation of $H(\lambda)$ compared to $P_2(\lambda)$ as we traverse a given contour. Unfortunately, the theorem developed in [66] cannot be used directly in our case because the hypotheses are not satisfied, but the argument can be modified and we can thereby deduce conditions on the parameter space which ensure stability. However, these conditions are not easy to satisfy in reality. Therefore, we will apply the same methods as in section 5.4.2 to study the stability.

Define

$$G(y) = |P_2(iy)|^2 - |Q_2(iy)|^2.$$

Then

$$G(y) = y^6 + n_2y^4 + n_1y^2 + n_0, \tag{5.11}$$

where

$$\begin{aligned} n_2 &= b_2 - 2b_1 \\ n_1 &= {b_1}^2 - 2b_2(b_0 + 2\alpha_1\alpha_2\alpha_3) \\ n_0 &= {b_0}^2 + 4b_0\alpha_1\alpha_2\alpha_3. \end{aligned}$$

Let $y^2 = x$. Then $G(y)$ becomes

$$G_1(y) = x^3 + n_2x^2 + n_1x + n_0. \tag{5.12}$$

With the same argument as in *Lemma* 5.4.2, we have:

Lemma 5.4.4 *Define*

$$\Delta = \frac{4}{27}{n_1}^3 - \frac{1}{27}{n_2}^2{n_1}^2 + \frac{4}{27}{n_2}^3n_0 - \frac{2}{3}n_2n_1n_0 + {n_0}^2.$$

Suppose that $n_0 > 0$. Then for system (5.10)

(I) Necessary and sufficient conditions for the cubic equation (5.12) to have at least one simple positive root for x are:

(i) either (a) $n_2 < 0$, $n_1 \geq 0$ and ${n_2}^2 > 3n_1$, or (b) $n_1 < 0$

and

(ii) $\Delta < 0$.

(II) Necessary and sufficient conditions for the cubic equations (5.12) to have no positive real roots for x are either,

(i) $3n_1 \geq {n_2}^2$

(ii) ${n_2}^2 > 3n_1$ and $\Delta > 0$ or

(iii) ${n_2}^2 > 3n_1$, $\Delta \leq 0$, $n_2 > 0$ and $n_1 > 0$.

Based on *Lemmas* 5.4.3 and 5.4.4, we obtain the following theorems.

Theorem 5.4.3 *For system (5.10), suppose that ${n_2}^2 > 3n_1$, $\Delta \leq 0$, $n_2 > 0$ and $n_1 > 0$. Then*

1) if $H(\lambda)$ is stable with $\tau = 0$ (i.e. $b_0 > 0$), it remains stable for all $\tau \geq 0$,

2) if $H(\lambda)$ is unstable with $\tau = 0$ (i.e. $b_0 \leq 0$) and $n_0 > 0$, it remains unstable for all $\tau \geq 0$.

Theorem 5.4.3 implies that there exists a certain case in which the condition for cancer growth or extinction of all cancer cells will remain unchanged even if we add the delay in the corresponding model with immune suppression. In such a case, we say the delay is harmless for the stability of the system.

Theorem 5.4.4 *For system (5.10), assume that either (a) ${n_2}^2 < 3n_1$ and $\Delta > 0$, or (b) $n_1 < 0$ and $\Delta < 0$. Then there exists a positive $\bar{\tau}$ such that*
(i) if $b_0 > 0$, the cancer-free equilibrium E_1 remains stable for $0 \leq \tau < \bar{\tau}$, and becomes unstable for all $\tau > \bar{\tau}$.
(ii) if $b_0 \leq 0$ and $n_0 > 0$, the cancer-free equilibrium E_1 remains unstable for $0 \leq \tau < \bar{\tau}$, and becomes stable for $\tau > \bar{\tau}$.
Moreover, in both cases, the cancer-free equilibrium will become unstable when the delay becomes sufficiently large.

As mentioned earlier, in the context of cancer models, stability switching as the delay is varied is very important since many cycle-phase-specific drugs retain the cells or trap them in a given phase, thus increasing the time a cell spends in a particular compartment. This analysis shows that care must be taken when trapping the cells in a compartment since the ultimate effect may be adverse: the cancer-free fixed point may switch from a stable equilibrium to an unstable one (see (i) of *Theorem* 5.4.4). This would mean that when treatment is stopped, the system would not move towards the disease-free state. On the other hand, it is possible to increase or decrease the resident time during the interphase to "unlock" a fixed point from its instability and to push it towards the stable range (see (ii) of *Theorem* 5.4.4).

5.4.5 Drug model in a non-delay case with immune suppression

Now we shall begin to consider the effect of drugs in the model along with the immune suppression when there is no delay, $\tau = 0$. We are interested in studying how the conditions

for the cancer growth or extinction are varied when we apply drugs to the model. In this case the system considered becomes:

$$\begin{aligned}
\dot{x}(t) &= -(\alpha_1+\delta_1)x(t) + s\alpha_3 z(t) - k_1 x(t)I(t) \\
\dot{y}(t) &= \alpha_1 x(t) - (\alpha_2+\delta_2)y(t) - k_2 y(t)I(t) - k_4(1-e^{-k_5 u(t)})y(t) \\
\dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3+\delta_3)z(t) - k_3 z(t)I(t) \\
\dot{I}(t) &= k + \frac{\rho I(t)(x+y+sz)^n}{a+(x+y+sz)^n} - (c_1 x(t) + c_2 y(t) + c_3 z(t) + \delta_4)I(t) - k_6(1-e^{-k_7 u(t)})I(t) \\
\dot{u}(t) &= -\gamma u(t).
\end{aligned} \tag{5.13}$$

Under this situation, $E_2(0,0,0,k/\delta_4,0)$ ia an equilibrium of this system with zero cancer and drug levels and a positive immune level. Again, in general there are other fixed points, but this fixed point is of particular interest since it represents a cancer and drug-free state. The Jacobian matrix about E_2 is

$$\begin{bmatrix}
-(\alpha_1+\delta_1+k_1k/\delta_4) & 0 & s\alpha_3 & 0 & 0 \\
\alpha_1 & -(\alpha_2+\delta_2+k_2k/\delta_4) & 0 & 0 & 0 \\
0 & 2s^{-1}\alpha_2 & -(\alpha_3+\delta_3+k_3k/\delta_4) & 0 & 0 \\
-c_1k/\delta_4 & -c_2k/\delta_4 & -c_3k/\delta_4 & -\delta_4 & k_6k_7k/\delta_4 \\
0 & 0 & 0 & 0 & -\gamma
\end{bmatrix}.$$

Clearly, $\lambda=-\gamma$, $\lambda=-\delta_4$ are two eigenvalues. The remaining eigenvalues are the same as the solutions to characteristic equation (5.7), that is,

$$\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0,$$

where n_2, n_1, n_0 are given in section 5.4.3. With the same argument as in section 5.4.3, we have the following lemma.

Lemma 5.4.5 *For system (5.13), the cancer-free equilibrium E_2 is locally asymptotically stable if and only if $b_0 > 0$.*

Comparing with *Lemma* 5.4.3 in section 5.4.3, *Lemma* 5.4.5 shows that the condition for the extinction of cancer cells in all phases remains the same, which implies that the drug does not have any effects on the stability of the cancer-free equilibrium. This is because the

cancer cells in the resting phase escape the action of the cycle-specific cytotoxic agents, and the drugs are only cytotoxic to the cells in the mitosis phase. This suggests that the immune therapy will be an optimal treatment to inhibit the growth of the cancer cells. Therefore, we have the following.

(i) When we include the immune suppression into the model, it will greatly help to inhibit the further growth of the cancer cells (see the first term of b_0).

(ii) If lymphocytes are produced at a sufficiently high rate (sufficiently large value of k) or are very effective in destroying the cancer cells in the resting phase (sufficiently high value of k_3) with a lower natural death rate (sufficiently small value of δ_4), then it becomes to easy to obtain conditions for the extinction of cancer cells ($b_0 > 0$) in all phases(sufficiently high value of $kk_3\delta_4^{-1}$ such that $\delta_3 + kk_3\delta_4^{-1} > \alpha_3$, i.e. $b_0 > 0$).

(iii) It follows from *Lemma* 5.4.5 that a necessary condition for the cancer growth is $b_0 \leq 0$, which implies that if lymphocytes lose the ability to recognize these cancer cells, the cancer cells will continue to reproduce at a larger rate and eventually dominate the normal tissues.

5.4.6 Drug model when $\tau > 0$ with immune suppression

When we add the effect of the delay in the model, we obtain

$$\begin{aligned}
\dot{x}(t) &= -\alpha_1 x(t) - \delta_1 x(t) + s\alpha_3 z(t) - k_1 x(t) I(t) \\
\dot{y}(t) &= \alpha_1 x(t-\tau) - (\alpha_2 + \delta_2) y(t) - k_2 y(t) I(t) - k_4 (1 - e^{-k_5 u(t)}) y(t) \\
\dot{z}(t) &= 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \delta_3) z(t) - k_3 z(t) I(t) \\
\dot{I}(t) &= k + \frac{\rho I(t)(x + y + sz)^n}{a + (x + y + sz)^n} - (c_1 x(t) + c_2 y(t) + c_3 z(t) + \delta_4) I(t) - k_6 (1 - e^{-k_7 u(t)}) I(t) \\
\dot{u}(t) &= -\gamma u(t).
\end{aligned} \tag{5.14}$$

Again E_2 is an equilibrium and its analysis is similar to the case of section 5.4.4. The system has the same equilibria as the system described in section 5.4.5, but again we focus on the cancer free equilibrium E_2.

In this case, the characteristic equation for the linearized equation about a fixed point E_2 is given by:

$$\begin{vmatrix} \lambda+\alpha_1+\delta_1+k_1k/\delta_4 & 0 & -s\alpha_3 & 0 & 0 \\ -\alpha_1 e^{-\lambda\tau} & \lambda+\alpha_2+\delta_2+k_2k/\delta_4 & 0 & 0 & 0 \\ 0 & -2s^{-1}\alpha_2 & \lambda+\alpha_3+\delta_3+k_3k/\delta_4 & 0 & 0 \\ c_1k/\delta_4 & c_2k/\delta_4 & c_3k/\delta_4 & \lambda+\delta_4 & -k_6k_7k/\delta_4 \\ 0 & 0 & 0 & 0 & \lambda+\gamma \end{vmatrix} = 0$$

Obviously, $\lambda = -\delta_4$, $\lambda = -\gamma$ are two eigenvalues. The remaining eigenvalues are given as the solutions to the characteristic equation

$$F(\lambda) = \lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 + 2\alpha_1\alpha_2\alpha_3 - 2\alpha_1\alpha_2\alpha_3 e^{-\lambda\tau} = 0,$$

where b_2, b_1, b_0 are given in section 5.4.4 and the stability analysis of the equilibria is same as $H(\lambda)$, and thus we state the appropriate theorems here.

Theorem 5.4.5 *For system (5.14), suppose that* ${n_2}^2 > 3n_1, \Delta \leq 0, n_2 > 0$ *and* $n_1 > 0$. *Then*

1) if $b_2b_1 > n_0$ *then* E_2 *remains stable for all* τ,

2) if $b_2b_1 < n_0$ *then* E_2, *it remains unstable for all* τ.

Theorem 5.4.6 *For system (5.14), assume that either (a)* $n_2 < 0$, $n_1 \geq 0$ *and* ${n_2}^2 > 3\xi_1$, *or (b)* $n_1 < 0$ *and* $\Delta < 0$. *Then there exists a positive* $\bar{\tau}$ *such that*

(i) if $b_2b_1 > b_0$ *then the equilibrium* E_2 *remains stable for* $0 \leq \tau < \bar{\tau}$, *and becomes unstable for all* $\tau > \bar{\tau}$,

(ii) if $b_2b_1 < b_0$ *then the equilibrium* E_2 *remains unstable for all* $\tau > \bar{\tau}$. *As* τ *varies from* 0 *to* $\bar{\tau}$, *at most a finite number of stability switches may occur.*

Theorem 5.4.6 shows that there are cases in which we can depend on to design a drug protocol. If we are in the stability switching region and the cancer-free equilibrium is unstable (see (ii) of *Theorem* 4.5.6), it may be possible to use the trapping mechanism to stabilize the cancer-free equilibrium. However, if we are certain that our parameters are in the stable region, we may choose a way to inhibit the activities of the lymphocytes in the resting phase.

5.5 Hopf bifurcation

With the aid of *Theorem* 1 in [18], it is also straightforward to check for possible Hopf bifurcations when we increase the delay τ. The importance of Hopf bifurcations in this context is that at the bifurcation point a limit cycle is formed around the fixed point, thus resulting in stable periodic solutions. The existence of periodic solutions is relevant in cancer models because it implies that the cancer levels may oscillate around a fixed point even in the absence of any treatment. Such a phenomenon has been observed clinically and is known as "Jeff's Phenomenon" [54]. In this section, we will prove that such Hopf bifurcation can occur. Now consider a general characteristic equation

$$\lambda^3 + r_2\lambda^2 + r_1\lambda + r_0 - s_0e^{-\lambda\tau} = 0. \tag{5.15}$$

Let $\lambda = u + iv$,$(u, v \in R)$ and rewrite (5.15) in terms of its real and imaginary parts as

$$\begin{aligned} u^3 - 3uv^2 + r_2(u^2 - v^2) + r_1u + r_0 &= s_0e^{-u\tau}\cos(v\tau), \\ 3u^2v - v^3 + 2r_2uv + r_1v &= -s_0e^{-u\tau}\sin(v\tau). \end{aligned} \tag{5.16}$$

Let $\bar{\tau}$ be such that $u(\bar{\tau}) = 0$. Then The above equations reduce to

$$\begin{aligned} -r_2\bar{v}^2 + r_0 &= s_0\cos(\bar{v}\bar{\tau}) \\ -\bar{v}^3 + r_1\bar{v} &= -s_0\sin(\bar{v}\bar{\tau}). \end{aligned} \tag{5.17}$$

It follows by taking the sum of squares that

$$\bar{v}^6 + ({r_2}^2 - 2r_1)\bar{v}^4 + ({r_1}^2 - 2r_2r_0)\bar{v}^2 + {r_0}^2 - {s_0}^2 = 0. \tag{5.18}$$

Suppose that $\bar{v}_1$ is the last positive simple root of equation (5.18). Then with this value of $\bar{v}_1$ (5.17) determine a $\bar{\tau}_1$ uniquely such that $u(\bar{\tau}_1) = 0$ and $v(\bar{\tau}_1) = \bar{v}_1$. To apply the Hopf bifurcation theorem as stated in Marsden & McCracken [69] we state and prove the following theorem.

Theorem 5.5.1 *Suppose that equation (5.18) has at least one simple positive root and $\bar{v}_1$ is the last such root. Then $iv(\bar{\tau}_1) = i\bar{v}_1$ is a simple root of equation (5.15) and $u(\tau) + iv(\tau)$ is differentiable with respect to τ in a neighborhood of $\tau = \bar{\tau}_1$.*

Proof. To show that $iv(\bar{\tau}_1) = i\bar{v}_1$ is a simple root, equation (5.15) can be written as $f(\lambda) = 0$ where

$$f(\lambda) = \lambda^3 + r_2\lambda^2 + r_1\lambda + r_0 - s_0 e^{-\lambda\tau}. \tag{5.19}$$

Any double root λ satisfies

$$f(\lambda) = 0, \ f'(\lambda) = 0,$$

where

$$f'(\lambda) = 3\lambda^2 + 2r_2\lambda + r_1 + \tau s_0 e^{-\lambda\tau}. \tag{5.20}$$

Substituting $\lambda = i\bar{v}_1$ and $\tau = \bar{\tau}_1$ into (5.20) and equating real and imaginary parts if $i\bar{v}_1$ is a double root, we obtain

$$\begin{aligned} -r_2\bar{v}_1^2 + r_0 &= s_0\cos(\bar{v}_1\bar{\tau}_1) \\ -\bar{v}_1^3 + r_1\bar{v}_1 &= -s_0\sin(\bar{v}_1\bar{\tau}_1) \end{aligned} \tag{5.21}$$

and

$$\begin{aligned} r_1 - 3\bar{v}_1^2 &= -\bar{\tau}_1 s_0\cos(\bar{v}_1\bar{\tau}) \\ 2r_2\bar{v}_1 &= \bar{\tau}_1 s_0\sin(\bar{v}_1\bar{\tau}). \end{aligned} \tag{5.22}$$

Now, equation (5.17) can be written as $F(\bar{v}_1) = 0$, where

$$F(v) = (-r_2v^2 + r_0)^2 + (-v^3 + r_1v)^2 - (s_0)^2 \tag{5.23}$$

$$F'(v) = 2(-r_2v^2 + r_0)(-2r_2v) + 2(-v^3 + r_1v)(-3v^2 + r_1). \tag{5.24}$$

By substituting (5.21) and (5.22) into (5.23), (5.24), we obtain

$$F(\bar{v}_1) = F'(\bar{v}_1) = 0.$$

Note that $\bar{v}_1$ is a double root of $F(\bar{v}_1) = 0$ and that $F(\bar{v}_1) = F'(\bar{v}_1) = 0$, which is a contradiction as we have assumed that $\bar{v}_1$ is a simple root of (5.18). Hence $i\bar{v}_1$ is a simple root of equation (5.15), which is an analytic equation. By using the analytic version of the implicit function theorem (Chow & Hale [16]), we can see $u(\tau) + iv(\tau)$ is defined and analytic in a neighborhood of $\tau = \bar{\tau}_1$. The proof is complete!

Next, to establish Hopf bifurcation at $\tau = \bar{\tau}_1$, we need to verify the transversality condition

$$\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} \neq 0.$$

By differentiating equations (5.16) with respect to τ and setting $u = 0$ and $v = \bar{v}_1$, we obtain

$$\begin{aligned} A\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} + B\frac{dv}{d\tau}|_{\tau=\bar{\tau}_1} &= -s_0\bar{v}_1\sin(\bar{v}_1\bar{\tau}_1) \\ -B\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} + A\frac{dv}{d\tau}|_{\tau=\bar{\tau}_1} &= s_0\bar{v}_1\cos(\bar{v}_1\bar{\tau}_1) \end{aligned} \tag{5.25}$$

where

$$\begin{aligned} A &= r_1 - 3\bar{v}_1^2 + s_0\bar{\tau}_1\cos(\bar{v}_1\bar{\tau}_1) \\ B &= -2r_2\bar{v}_1 + s_0\bar{\tau}_1\sin(\bar{v}_1\bar{\tau}_1). \end{aligned}$$

Solving for $\frac{du}{d\tau}$, $\frac{dv}{d\tau}$ form (5.24) with the help of (5.17), we have

$$\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} = \frac{\bar{v}_1^2[3\bar{v}_1^4 + 2({r_2}^2 - 2r_1)\bar{v}_1^2 + {r_1}^2 - 2r_2r_0]}{A^2 + B^2} \tag{5.26}$$

Let $z = \bar{v}_1^2$ then equation (5.18) reduces to

$$\Phi(z) = z^3 + ({r_2}^2 - 2r_1)z^2 + ({r_1}^2 - 2r_2r_0)z + {r_0}^2 - {s_0}^2.$$

Hence

$$\frac{d\Phi}{dz} = 3z^2 + 2({r_2}^2 - 2r_1)z + {r_1}^2 - 2r_2r_0.$$

Since $\bar{v}_1^2$ is the last positive single root of equation(5.18), then

$$\frac{d\Phi}{dz}|_{z=\bar{v}_1^2} > 0.$$

Therefore,

$$\frac{du}{d\tau}|_{\tau=\bar{\tau}_1} = \frac{\bar{v}_1^2}{A^2 + B^2}\frac{d\Phi}{dz}|_{z=\bar{v}_1^2} > 0.$$

We summarize the preceding details in the following theorem.

Theorem 5.5.2 *Suppose that (5.18) has at least one simple positive root and $\bar{v}_1$ is the last such root. Then a Hopf bifurcation occurs as τ passes through $\bar{\tau}_1$. On the other hand if (5.16) has no positive real roots then the disease free fixed point is locally asymptotically stable for all values of τ.*

5.6 Numerical results

In this section, we will use the original mathematical model to determine numerical solutions for the population's stem cells. To do this, we first find reasonable estimates for the values of the parameters from [104]. For the abnormal cells, we will use the estimates for the parameters of $\tau = 14\,hr(0.6\,days)$, $x(0) = y(0) = 1$ x $10^6\,cells$, $z(0) = 2$ x 10^6, $\alpha_1 = 0.84\,day^{-1}$, $\alpha_2 = 0.9\,day^{-1}$, $\alpha_3 = 0.024\,day^{-1}$, $\delta_1 = 0.11\,day^{-1}$, $\delta_2 = 0.67\,day^{-1}$, $\delta_3 = 0.056\,day^{-1}$.

The MATLAB simulations in *Figure* 5.2, running with a delay parameter equal 0.6 days show that a cancer population in the absence of an immune suppression decays with any delays, which implies that the stability of the cancer-free equilibrium $E_0(0,0,0)$ is independent of delays.

Next, we would like to examine the stability switches for cancer growth. Thus we can use the information about the drug-free model to design a drug protocol. Here we choose the non-dimensional parameter values set at $\alpha_1 = 0.84$, $\delta_1 = 0.12$, $\alpha_2 = 0.9$, $\delta_2 = 0.32$, $\alpha_3 = 0.87$, $\delta_3 = 0.25$. We can use now *Theorem* 5.4.2 in section 5.4.2 to check the stability of the cancer-free equilibrium. In this case, cancer cells begin to grow in positive time. The MATLAB simulations in *Figure* 5.3-5.5, running with three different delay parameters show that a cancer population without any treatment begins to grow with a small delay below the bifurcation point (about 60 days) and oscillates periodically at the bifurcation point. They demonstrate that oscillatory instability can be stabilized by increasing the cell cycle time.

Finally, we now would like to examine the stability of the steady state with immune suppression. The immune system is made up of many different types of cells and each cell has different functions. Some very important cell types are the lymphocytes. The helper T cells and the cytotoxic T cells are two subcategories of the T cells which is a subset of the lymphocytes. In this chapter, we only focus on the cytotoxic T cells as the primary representation of the immune system given its importance in the fight against cancer. For more detailed information about the immune system, the reader is referred to [104]. Here the parameter values of lymphocytes are chosen from [104,109]. Therefore, we use the estimates of $x(0) = y(0) = I(0) = 1$ x $10^6\,cells$, $z(0) = 2$ x 10^6, $k_1 = k_2 = k_3 = 2.16$

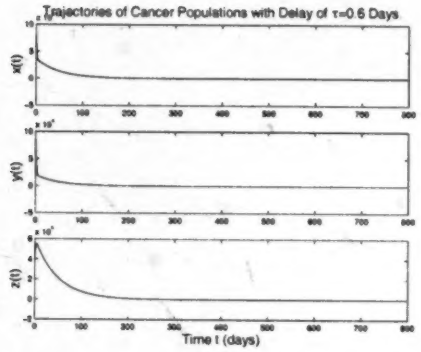

Figure 5.2: A solution for model (5.3) in the absence of any treatments with $x(0) = y(0) =$ 1 x $10^6\, cells$, $z(0) = 2$ x $10^6\, cells$, $\alpha_1 = 0.84\, day^{-1}$, $\alpha_2 = 0.9\, day^{-1}$, $\alpha_3 = 0.024\, day^{-1}$, $\delta_1 = 0.11\, day^{-1}$, $\delta_2 = 0.67\, day^{-1}$, $\delta_3 = 0.056\, day^{-1}$. Here the cancer-free equilibrium $E_0(0, 0, 0)$ is stable for any delays, which implies that the stability is independent of cell cycle duration and cancer populations eventually go extinct in positive time (see *Theorem* 5.4.1).

x $10^{-7}\, cell^{-1}\, day^{-1}$, $c_1 = c_2 = c_3 = 3.42$ x $10^{-10}\, cell^{-1}\, day^{-1}$, $k = 1.3$ x $10^4\, cell\, day^{-1}$, $n = 3$, $\rho = 0.3\, day^{-1}$, $a = (0.3$ x $10^6 cell)^3$, $k_4 = k_6 = 0.02\, day^{-1}$, $k_5 = k_7 = 0.03\, g^{-1}$, $\delta_4 = 0.04\, day^{-1}$, $\gamma = 0.7\, day^{-1}$. $u(0) = 4$ x $10^6\, g$.

With the non-dimensional parameter values set at $\alpha_1 = 0.84$, $\alpha_2 = 0.9$, $\alpha_3 = 0.87$, $k_1 = 0.02$, $k_2 = 0.08$, $k_3 = 0.02$, $c_1 = 0.02$, $c_2 = 0.08$, $c_3 = 0.02$, $\delta_1 = 0.12$, $\delta_2 = 0.32$, $\delta_3 = 0.25$, $\delta_4 = 0.04$,$a = 0.5$, $\rho = 0.2$, $k = 0.36$, we can use *Lemma* 5.4.3 and *Theorem* 5.4.3 to check the stability of the steady states of the model described in section 5.4.3-5.4.4. Note that in the case of no immune suppression with these same parameter values, cancer populations begin to grow eventually. The MATLAB simulations in *Figure* 5.6 show that the lymphocytes eventually inhibit the cancer growth and demonstrate a effectively treatment,which is consistent very well with our analysis in the models.

5.7 Discussion

In this chapter, we studied the cycle-specificity of chemotherapy to the G_0 model. Now we can answer the questions we listed at the beginning. In the absence of any treatments,

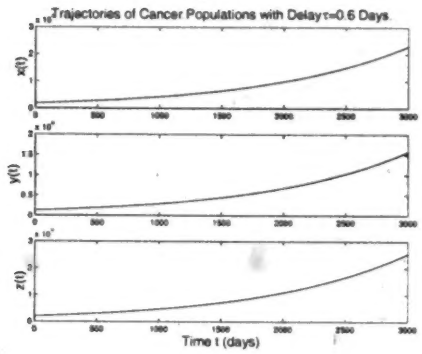

Figure 5.3: A solution for model (5.3)in the absence of treatments with $x(0) = y(0) = 1$ x $10^6\,cells$, $z(0) = 2$ x $10^6\,cells$, $\alpha_1 = 0.84\,day^{-1}$, $\alpha_2 = 0.9\,day^{-1}$, $\alpha_3 = 0.87\,day^{-1}$, $\delta_1 = 0.12\,day^{-1}$, $\delta_2 = 0.32\,day^{-1}$, $\delta_3 = 0.25\,day^{-1}$. Here the cancer-free equilibrium $E_0(0,0,0)$ is unstable, which implies cancer populations begin to grow with a small delay (see 2) of *Theorem* 5.4.2).

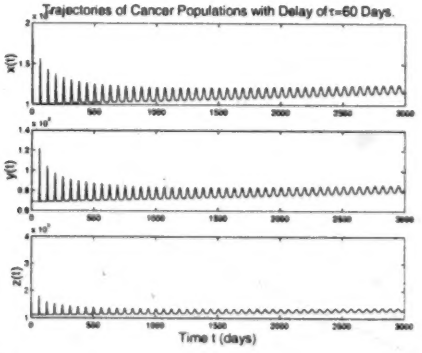

Figure 5.4: A solution for model (5.3) in the absence of any treatments with the same parameters in *Figure* 5.3, but with a critical delay. Here the level of cancer populations begin to oscillate and cancer is in the control by increasing the cell cycle duration to a critical value (see 2) of *Theorem* 5.4.2).

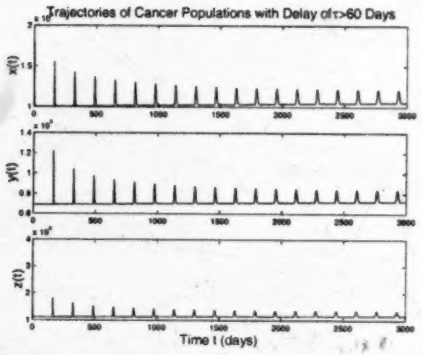

Figure 5.5: A solution for model (5.3) in the absence of any treatments with the same parameters in *Figure* 5.3, but with a big delay. Here we can stabilize the cancer-free equilibrium E_0 by increasing the cell cycle duration and the cancer is in the control(see 2) of *Theorem* 5.4.2).

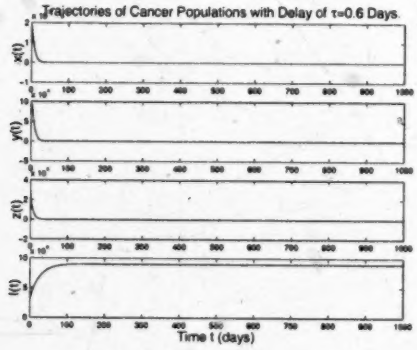

Figure 5.6: A solution for model (5.8) in the case of immune suppression with the same parameters in *Figure* 5.3, along with $k_1 = 0.02$,$k_2 = 0.08$, $k_3 = 0.02$, $c_1 = 0.02$, $c_2 = 0.08$, $c_3 = 0.02$, $\delta_4 = 0.04$,$a = 0.5$, $\rho = 0.2$, $k = 0.36$. Here the stability of cancer-free equilibrium is independent of the parameter delay and it becomes stable under the treatment of immune suppression (Note that the equilibrium is originally unstable without any treatments), which implies the lymphocytes help the body fight and destroy the cancer cells and eventually keep the body healthy(See *Lemma*5.4.3 and *Theorem* 5.4.3).

we see that cancer growth mainly depends on the death rate of cells in the resting phase and the reproduction rate at which cells in the resting phase go into the cell cycle (see *Lemma* 5.4.1). Cancer will begin to grow if the reproduction rate is greater than the death rate of cancer cells in the resting phase, which implies that without any treatment cancer will grow, accumulate and eventually become fatal to the body. Cell cycle duration is an important factor to give rise to oscillation of solutions. When including the cell cycle time into consideration, we determined those situations where the cell cycle time delay is harmless and in which cases, stability switches occur and thus periodic solutions exist. Based on all these dynamical behaviors and the critical cell cycle time value we found here, a better drug protocol may be designed and delivered to treat the disease (see the *Theorems* 5.4.2,5.4.4 and 5.4.6).

When disease develops, the immune system is a natural force to fight against the disease. Taking the immune suppression into account in the model, we showed that it will greatly help to inhibit the growth of cancer cells (see *Lemma* 5.4.3), especially, if the lymphocytes are rapidly producing and are very effective in combining with cancer cells in order to destroy them, there is little chance for the cancer cells to reach maturity. Unfortunately, this may only happen at the beginning of the disease onset and we may depend on drugs to inhibit the growth of cancer cells if the disease gets worse and the lymphocytes lost their ability to recognize these abnormal cells .

Finally, we consider the application of drugs to the model. We demonstrated that the drug does not change the stability of cancer-free equilibrium compared with other cases we studied (see *Lemma* 5.4.4). This is because cancer cells in the resting phase escape the action of cycle-specific cytotoxic agents. However, drugs destroy cells in other phases and this will help to inhibit the further development of the disease. The study of this case suggests that immune therapy may be a natural and optimal treatment to inhibit the growth of cancer cells in order to well control the disease. Also, we observed periodic solutions for some parameter values through a Hopf bifurcation (see *Theorem* 5.5.2). Periodic tumors arise from time to time in patients. The existence of periodic solutions in our system implies that periodic tumor growth may be uncorrelated with the administration of chemotherapy. This case is referred to as Jeff's phenomenon.

Our model presented here is very simple but gives us interesting information about the dynamics of the system. The inclusion of a quiescent phase into consideration does give us a deep insight into the mechanism of disease development and help us understand how the resistant population contributes to the eradication of the disease. Our simulations are consistent well with the analysis we carried out in the model and the analysis provided a more rational basis for the design of anti-cancer drugs based on the mathematical relation between the dynamical variables involved in the progression of disease. Here we must point out there a few features we consider significant that have not been included in our model. For example the inclusion of another delay in the cell cycle might be pertinent as we separate the phases of the cycle to be more precise about the model action of the drugs on the different phases, or that these delays may be a function of the drug. The immune system is a very complicated entity, and in this chapter we have merely touched the surface of the interactions and processes involved in the immune system response. A more careful study and detailed modeling of the interaction is another avenue of possible future research.

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